"FORMULATION AND EVALUATION OF SUSTAINED RELEASE CYCLOBENZAPRINE HYDROCHLORIDE CAPSULES"

A dissertation submitted to

THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI.

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY IN PHARMACEUTICS

BY

REG.NO: 26091382

Under the Guidance of

Mrs. T. SUDHAMANI., M.PHARM., (Ph.d).,

OCTOBER -2011

THE ERODE COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

ERODE -638112, TAMILNADU

DEDICATED TO MY BELOVED PARENTS, TEACHERS AND FRIENDS

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This is to certify that the investigation in this thesis entitled **FORMULATION AND EVALUATION OF SUSTAINED RELEASE CYCLOBENZAPRINE HYDROCHLORIDE CAPSULES"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai. For partial fulfillment of the award of degree of **Master of pharmacy** in P**harmaceutics** was carried out by **Reg. No: 26091382** in the department of pharmaceutics**, The Erode College of pharmacy and Research Institute, Erode,** under my guidance and supervision.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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Date: **Dr. V. Ganesan, M.Pharm., Ph.D.,**

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation described in this thesis entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE CYCLOBENZAPRINE HYDROCHLORIDE CAPSULES"** submitted in partial fulfillment of the requirements for the Degree Of **Master of Pharmacy** in **PHARMACEUTICS** was carried out in the laboratories of The Erode College Of Pharmacy and Research Institute, Erode by **Regd.No.26091382** under the guidance of **Mrs. T. Sudhamani, M.Pharm., (Ph.D)., The Erode College Of Pharmacy and Research Institute**, Erode, during the academic year 2010-2011.

Place: Erode

Date: **PRINCIPAL**

DECLERATION

The research work embodied in this dissertation work entitled **"FORMULATIONAND EVALUATION OF SUSTAINED RELEASE CYCLOBENZAPRINE HYDROCHLORIDE CAPSULES"** was carried out by me in the **Department of Pharmaceutics**, **The Erode College of Pharmacy and Research Institute, Erode**, under the direct supervisionof Mrs. T. Sudhamani**, M.Pharm., (Ph.D)., Dept.of Pharmaceutics, The Erode College of Pharmacy and Research Institute, Erode – 638 112.**

This dissertation submitted to **The TamilNadu Dr. M.G.R. Medical University**, **Chennai,** as a partial fulfillment for the award of **degree of Master of Pharmacy** in **Pharmaceutics** during the academic year 2009 – 2011.

The work is original and has not been submitted in part or full for the award of any other Degree or Diploma of this or any other University.

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CONTENTS

LIST OF ABBREVIATIONS

Mg	Milligram
Gm	Gram
Kg	kilogram
Ml	Milliliter
Cm	Centimeter
Nm	Nanometer
Sec	Second
µg/ml	Microgram per ml
Fig	Figure
MDDS	Modified Drug Delivery System
FTIR	Fourier Transform Infrared
BP	British Pharmacopoeia
USP	United State Pharmacopoeia
rpm	Rotations Per Minute
GIT	Gastrointestinal tract
DRR	Drug remaining to be release
% DR	Percentage drug release
% CDR	Percentage Cumulative drug release
SR	Sustained release
MEC	Minimum effective concentration
SEM	Scanning Electron Microscopy
UV	Ultra-violet spectroscopy
λ_{max}	Absorption maxima
v/w	volume/weight
w/w	weight/weight
R^2	Regression coefficient
Mins	minutes
hr	Hour
No	Number

LIST OF FIGURES / PHOTOGRAPHS

LIST OF TABLES

LIST OF GRAPHS

LIST OF SPECTRA

I. INTRODUCTION

An ideal drug delivery system provides treatment for acute diseases or chronic illness to the patients for many years. A number of oral dosage forms are available, some are liquids (e.g., syrups, elixirs, tinctures, suspensions, and emulsions), whereas the most common ones are solids (e.g., tablets and capsules). Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called conventional dosage forms. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of modified drug delivery system. The goal in designing modified delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action or reducing the dose required or providing uniform drug delivery. [1]

The term 'Modified Release' is used to describe products that alter the timing and/or the rate of release of the drug substance. The USP defines a modified drug delivery system "as one for which the drug release characteristics of time course or location of drug release, or both are chosen to accomplish objectives of therapeutic effectiveness or convenience not fulfilled by conventional dosage forms such as solution, ointments, or promptly dissolving dosage forms as presently recognized".[2]

1.1 TYPES OF ORAL DRUG DELIVERY SYSTEMS[3]

Oral drug delivery systems (ODDS) are divided into

1. Immediate release drug delivery systems
2. Modified release drug delivery systems

1.1.1) IMMEDIATE RELEASE DRUG DELIVERY SYSTEMS

Immediate release drug delivery systems are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug

effectiveness or increased incidence of side effects. Administration of the drug delivery systems several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion.

The limitations associated with such a conventional dosage form; [4]

- Poor patient compliance.
- Difficult to achieve steady-state plasma concentration.
- The unavoidable fluctuations in the drug concentration may lead to under-medication or over- medication.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index.

1.1.2) MODIFIED RELEASE DRUG DELIVERY SYSTEMS:

Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. Modified drug delivery systems sophisticated and take into account pharmacokinetic principles, specific drug characteristics, and variability of response among individuals with different medical conditions. These systems are design to deliver drugs at a specific site or over a period of time after administration, or at a specific location of the body. Administration

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release

B) Extended release

i) Sustained release

ii) Controlled release

C) Site specific targeting

D) Receptor targeting.

A) Delayed Release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Extended Release

Oral Drug Delivery Systems allows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

i) Sustained release

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

ii) Controlled release

Dosage form is generally accomplished by attempting to obtain "zero- order" release from the dosage form which independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained Release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent).

C) Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.2 Oral Controlled release Drug Delivery systems[2, 5]

The oral route of drug delivery is typically considered the preferred and most patient-convenient means of drug administration. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentrations in vivo. The reality is that many compounds are either incompletely or ineffectively absorbed after oral administration (i.e., bioavailability is an issue), or that the required dosing frequency is too short to enable once- or twice-daily administration (i.e., pharmacokinetic half-life is an issue). Lead optimization typically addresses such shortcomings during a discovery program; however, in many cases it is not possible to identify an appropriate clinical candidate with the requisite "ideal" physicochemical and/or pharmacokinetic properties. For clinical research phase drug candidates, or drugs already marketed, the opportunity for enhancing their clinical pharmacology profile after oral administration through attainment of more optimal blood drug concentration-time profiles should always be considered**.**

The development of a pharmaceutical product for oral delivery, irrespective of its physical form (solid, semisolid or liquid), involve varying extent of optimization of dosage form characteristics within the inherent constraints of gastrointestinal (GI) physiology.

Oral controlled release drug delivery is thus a drug delivery system that provides the continuous oral delivery of drug at the predictable and reproducible kinetics for predetermined period throughout the course of gastrointestinal transit. Also included are systems that target the delivery of drug to a specific region within the gastrointestinal tract for either a local or a systemic action. For oral controlled administration of drugs, several research and development activities have shown encouraging signs of progress in development of controlled release dosage forms as well as in the search for new approaches to overcome the potential problems associated with oral drug administration.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of mode of delivery (immediate, sustained or

controlled release) and the design of dosage form (solid, dispersion or liquid) must be developed within intrinsic characteristic of gastrointestinal (GI) physiology.

1.2.1. Gastrointestinal Anatomy and Physiology [4,6,7,8]

Drug Absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

The oral route of drug administration is most common for systemically acting drugs and therefore, more emphasis will be given to gastrointestinal (GI) absorption of drugs. Drug administered orally is pass from various part of GI tract (stomach, small intestine, large intestine), which differ from each other in terms of anatomy, function, secretion and pH.

- **Stomach:**

The stomach is an organ with a capacity for storage and mixing. The stomach lining is devoid of villi but consist of considerable number of gastric pits that contribute to the storage capacity of stomach.

Under physiological conditions, the gastric absorption of most drug is insignificant as a result of its limited surface area (0.1-0.2 m^2) covered by a thick layer of mucus coating, lack of villi on the mucosal surface, and short residence time of most drugs in the stomach. Its acidic pH (1-3), due to secretion of HCl, favors absorption of acidic drugs if they are soluble in gastric fluid since they are unionized to the large extent in such a pH. The gastric pH aids dissolution of basic drugs due to salt formation and subsequent ionization which are therefore absorbed to a lesser extent from stomach because of the same reason.

- **Small intestine:-**

It is the major site for absorption of most drugs due to its large surface area (200 m^2). The folds in the intestinal mucosa, called as the folds of Kerckring, result in the three fold increase in surface area. The surface of these folds possess finger like projection called as villi which increase surface area 30 times. From the surface of villi protrude several microvilli resulting in 600 times increase in surface area. Blood flow to the small intestine is 6-10 times that of stomach. Moreover, the pH range of 5-7.5 is most favorable of most drugs to remain unionized. The peristaltic movement of

intestine is slow, transit time is long, and permeability is high. Thus, a Contribution of all the above factors make intestine best site for absorption of most drugs.

Large intestine:-

Its length and mucosal surface area is very small (0.15 m^2) in comparison to small intestine and thus absorption of drugs from this region is insignificant. Its contents are neutral or alkaline. The main role of large intestine is in the absorption of water and electrolytes. However, because of the long residence time (6-12 hrs), colonic transit may be important in the absorption of some poorly drugs and sustain release dosage form.

- **Gastric emptying:-**[9]

It is the process of passage from stomach to the small intestine, can also be a rate limiting step in drug absorption because the major site for drug absorption is intestine. Thus, generally speaking, rapid gastric emptying increases bioavailability of drugs.

Gastric emptying of a drug is delayed by co-administrating food because unless the gastric content are fluid enough or the size of the solid particles is reduced below to 2 mm, its passage through the pylorus into the intestine is not possible.

For better absorption, the gastric emptying can be promoted by taking the drugs on empty stomach.

- **Gastro intestinal transit time :-** [10,11]

Small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption.

Residence time depends upon the intestinal motility or contractions. The mixing movement of the intestine that occurs due to peristaltic contraction promotes drug absorption, firstly, by increasing the drug intestinal membrane contact, and secondly, by enhancing the drug dissolution especially of poorly soluble drugs.

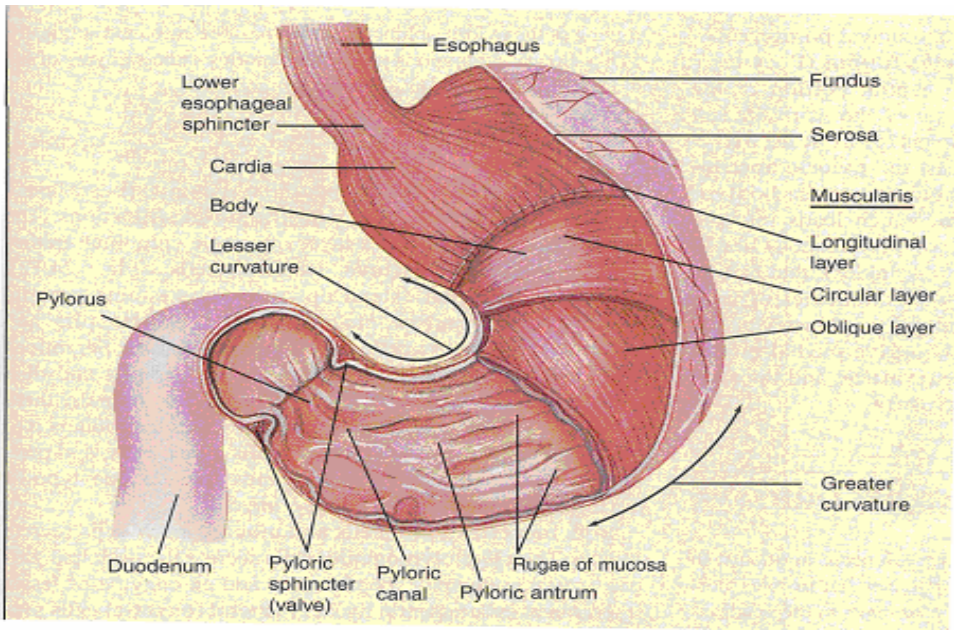


Fig 1: Stomach.

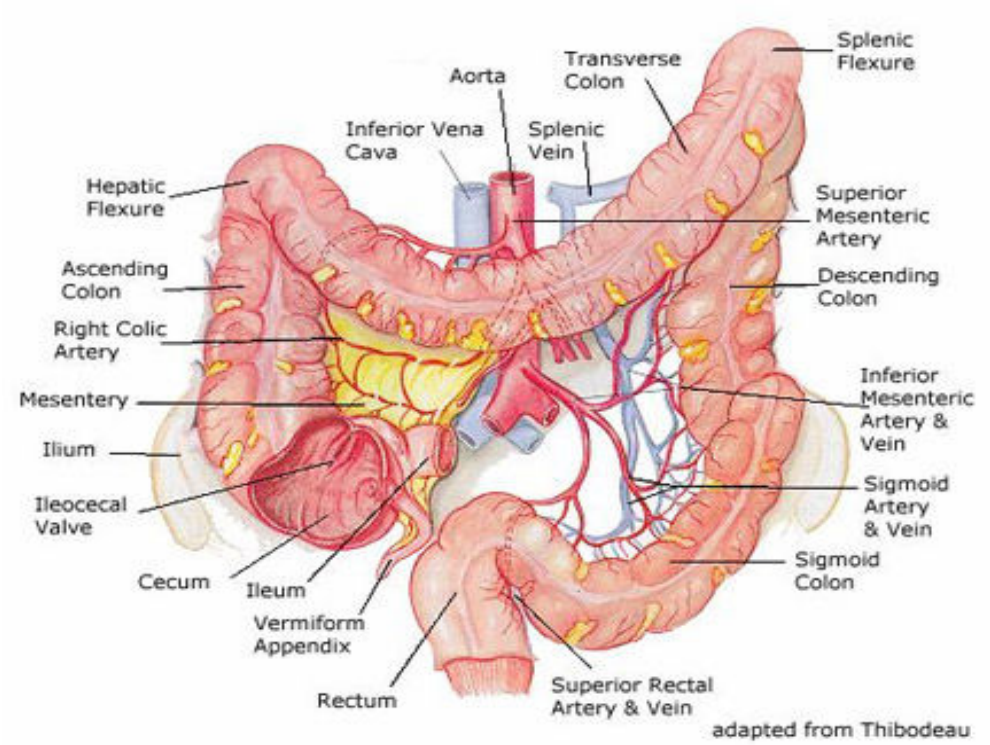


Fig 2: Parts of Large Intestine.

Table no. 1: APPROXIMATE pH AND TRANSIT TIME WITH IN THE GASTROINTESTINAL TRACT

Part	pH	Transit time (Hours)
Stomach	1.0-3.0	1-5
Duodenum	4.0-6.5	5min
Jejunum	5.0-7.0	2
Ileum	6.0-8.0	3-6
Caecum	6.0-8.0	0.5-1.0
Colon	6.0-8.0	6-12
Rectum	6.0-8.0	6-12

1.3 SUSTAINED RELEASE CONCEPT[3, 5]

Sustained release, sustained action, prolonged action controlled release, extended action , timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of single dose.

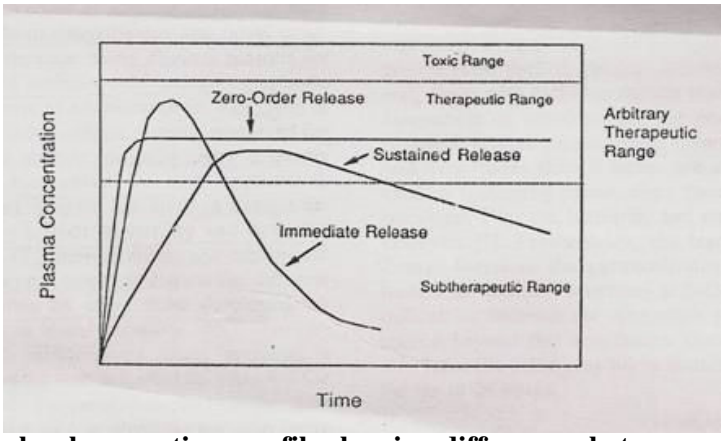


Fig3: Drug level verses time profile showing differences between zero order, controlled release, slow first order sustained release and release from conventional tablet.

Sustained release and controlled release will represent separate delivery processes; sustained release constitutes any dosage form that provides medication

over an extended period of time. Controlled release however, denotes that system is able to provide same actual therapeutic control, whether this be temporal nature, spatial nature or both .In other words, the system attempts to control drug concentration in target tissue. This correctly suggests that there are sustained release systems that cannot be considered as controlled release.

In general, the goal of sustained release dosage form is to maintain therapeutic blood level or tissue level of the drug for extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes of the amount of drug in the delivery system(i.e.; a constant release rate).Sustained release systems generally don't attain this type of release and usually try to – zero order release by providing drug in a slow first order fashion(i.e.; concentration dependent).

Oral ingestion has been the most convenient and commonly employed route of drug delivery. Indeed for sustained release systems, the oral route of administration has received the most attention with respect to research on physiological and drug constraints as well as designing and testing of products.

With most of orally administered drugs targeting is not primary concern, and it is usually intended for drugs to permeate to the general circulation and perfuse to other body tissues(the obvious exception being medication intended for local gastrointestinal tissue treatment),for this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels, which in turn promotes greater concentrations of the drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended.

An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. In this case the drug blood level reached and time required to reach that level depend on the dose and dosing interval. There are several potential problems inherent in multiple dose therapy. If the dosing interval is not appropriate for the biological half life of the drug, large peaks and valleys in the drug blood level may result. For example the drug with short half life requires frequent dosing to maintain constant therapeutic levels. The drug blood level may not

be within the therapeutic range at sufficiently early times, an important consideration for certain disease state. Patient non compliance with the multiple dosing regimen can result in failure of this approach.

1.3.1 Rationale of sustained drug delivery [12, 13]

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties.

As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval© can vary and, for each drug, there exist a therapeutic window of plasma concentration, below which therapeutic effect is in sufficient, and above which toxic side effect are elicited. This is often defined as the ratio of median lethal dose (LD50) to median effective dose (ED50)

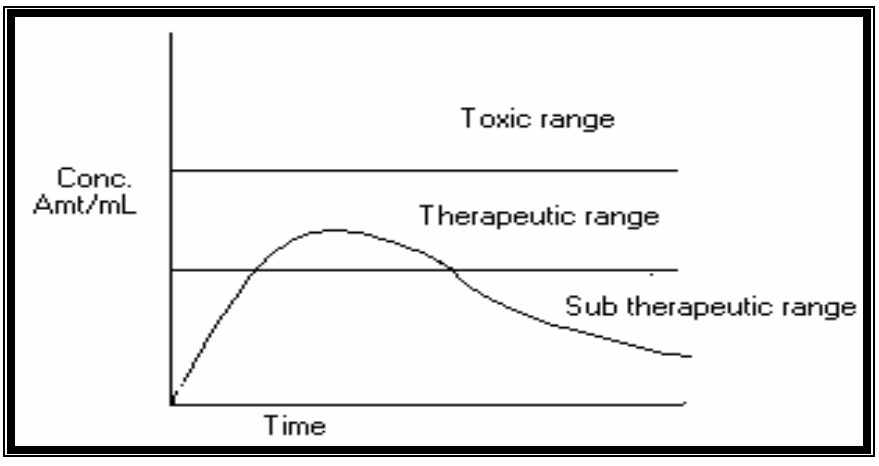


Fig 4: A hypothetical plasma concentration-time profile from oral Sustained release dosage formulations.

Potential advantages of sustained drug delivery:

1. Patient compliance due to reduction in the frequency of designing.

    a) Employ minimum drug

    b) Minimize or eliminates local and systemic side effects.

    c) Obtain less protestations or deduction in drug activity with chronic use.

    d) Minimize drug accumulation with chronic dosing.

2. Improve efficacy in treatment.

    a) Cure or controlled confirm more promptly.

    b) Improve control of condition i.e.; reduce fluctuation in drug level.

    c) Improve bioavailability of some drugs.

    d) Make use of special effects.

    e.g.: sustained release aspects for morning.

Disadvantages of sustained release dosage forms:

a) They are costly.

b) Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.

c) Poor systemic availability in general.

d) Effective drug release period is influenced and limited by GI residence time.

1.3.2 Classification of oral sustained/controlled release systems[14, 15]

A. **Continues release systems**

1. Dissolution controlled release systems
   a) Matrix type b) reservoir type
2. Diffusion controlled release systems
   a) Matrix type b) reservoir type
3. Dissolution and diffusion controlled release systems

4. Ion exchange resins drug complexes

5. Slow dissolving salts and complexes

6. pH dependent formulations

7. Osmotic pressure controlled systems

8. Hydrodynamic pressure controlled systems

B. **Delayed transit and continuous release systems**

1. Altered density systems

I. High density

II. Low density

III. Floating

2. Muco- adhesive systems

3. Size based systems

C. **Delayed released systems**

1. Intestinal release systems
2. Colonic release systems

Diffusion controlled systems:

The basic mechanism of drug release from these two systems is fundamentally different besides these simple systems, combination of reservoir and monolithic systems also exist in practice.

Diffusion systems are characterized by release rate of drug is dependant on its diffusion through inert water insoluble membrane barrier.

There are basically two types of diffusion devices.

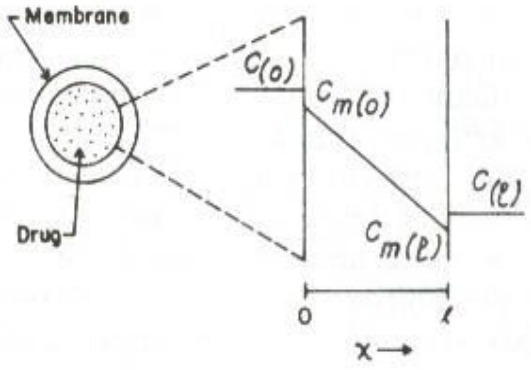
I. Reservoir devices

II. Matrix devices

- **Reservoir Devices:**

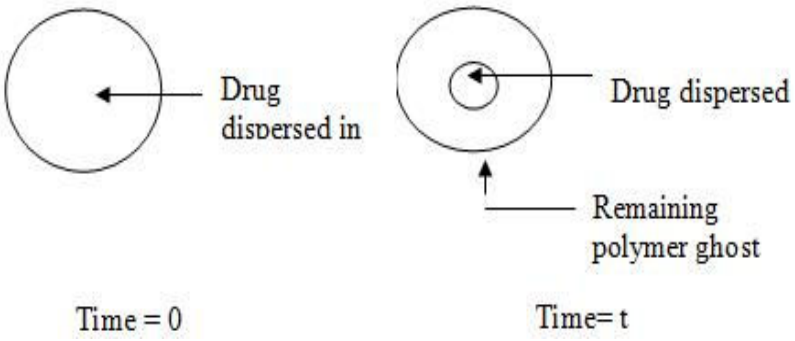
Reservoir Devices are those in which a core of drug is surrounded by polymeric membrane. The nature of membrane determines the rate of release of drug from system. The process of diffusion is generally described by following equation.

$$dMt/dt = ADK\,\Delta C/d$$



- **Matrix devices**

A matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer. Matrix diffusion system before release (time =0) & after partial drug release (time = t).



In this model drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix. This process continues with the interface between bathing solution and the solid drug moving controlled, the rate of dissolution of drug particles within the matrix must be faster that the diffusion rate of dissolved drug leaving matrix.

Osmotic controlled release systems:

Osmotic controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active ingredients. Drug delivery from these systems to a large extent is independent of physiological factors of the gastro intestinal tract and these systems is governed by various formulation factors such as solubility and osmotic pressure of the core component, size of the delivery orifice and nature of the rate controlling membrane. Drug release from this system is independent of pH and other physiological parameter to a larger extent and it is possible to modulate the release characteristics.

1.3.3 Factors Affecting Sustained Release Dosage Forms[16, 17]

The design of sustained release delivery system is subjected to several variables of considerable importance. Each of these variables is interrelated, and this imposes certain constraints upon choices for the route of delivery, the design of delivery systems, and the length of therapy. Of particular importance interest to the scientist designing the system are the constraints imposed by the properties of the drug. These properties have the greatest effect on the behaviors of the drug in the delivery systems and the body.

Factors governing the design of sustained /controlled release dosage forms.

A. Physico chemical factors

1. Aqueous solubility
2. Partition coefficient
3. Molecular size
4. Drug Stability
5. Protein binding
6. Dose size

B. Biological factors

1. Absorption
2. Distribution

3. Metabolism
4. Elimination
5. Duration of action
6. Margin of safety
7. Side Effects
8. Diseased state

A) PHYSICO CHEMICAL PROPERTIES

a) Dose Size:

In general, dose strength of 1.0g is considered maximum for a controlled release drug delivery systems.

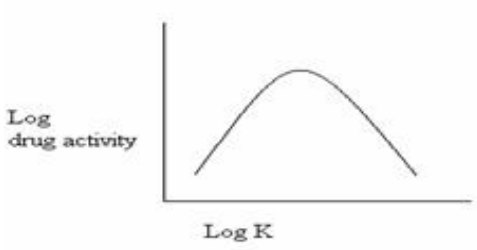
b) Aqueous Solubility:

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes. Drugs aqueous solubility will generally be decreased by conversion to an unchanged form, for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml.

c) Partition Coefficient:

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability.

Typical relationship between drug activity and partition Coefficient K, generally known as Hansch Correlation and is as follows;



d) Pka:

The relationship between PKa of compound and absorptive environment, presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form

e) Drug Stability:

Orally administered drugs can be subject to both acid, base hydrolysis and enzymatic degradation. Drugs unstable in GI pH, eg: propantheline can be designed for sustained delivery in intestine with limited or no delivery in stomach. On the other hand, a drug unstable in intestine, eg: probanthine can be formulated as gastro retentive dosage form.

f) Molecular size and diffusivity:

The ability of drug to diffuse through membranes it's so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight).

Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm2 / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 $cm^{2/}$sec. Thus high molecular weight drugs display very slow release kinetics in sustained release device using diffusion.

g) Protein binding:

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

Extensive binding to plasma proteins will be evidenced by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery

B) BIOLOGICAL FACTORS:

a) Biological Half Life:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

b) Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

c) Distribution:

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

d) Metabolism:

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic process

device a specific period, allowing more complete conversion of the drug to its metabolite.

e) Side effects and safety considerations:

For some drugs the incidence of side effects in addition to toxicity, is believed to be a function of plasma concentration. A controlled- release system can, at times, minimize side effects for a particular by controlling it's plasma concentration and using less total drug over the time course of therapy.

The most widely used measure of the margin of safety of a drug in it's therapeutic index, TI.

$$TI = LD_{50}/ED_{50}$$

Where,

LD_{50} = median lethal dose,

ED_{50} = median effective dose.

For very potent drugs, where therapeutic concentration range is narrow, the value of TI is small. In general larger the value of TI the safer the drug. Drugs with very small values of TI usually are poor candidates for formulation into controlled release products. Primarily because of technological limitations of precise control over release rates. A drug is considered relatively safe if it's TI value exceeds 10.

Eg: Drugs with values of TI< 10 are Apobarbital, Phenobarbital, Digitoxin, Digoxin.

f) Disease state:

Disease state and circadian rhythm are not drug properties how ever in few instances they are equally important as drug properties in considering drug for controlled release. A case in point is rheumatoid arthritis, for which aspirin is still a drug of choice. Normally aspirin would not be considered to be a likely candidate for sustained release because it's biological half life is 6 hours.

Initially the ultimate criterion for a sustain release tablet is to achieve a blood level and the drug comparable to that of liquid product administered every 4 hrs. To this end, prolong release dosage forms are designed to release the drug so as to provide a drug level within the therapeutic range for 8 to 12, with a single dose rather

than a dose every 4 hrs. No prolonged drug forms have without disadvantages. Since gastrointestinal tract is not uniform. If drug release was more slowly then not receive proper benefit of response. This is especially true for older people whose gastrointestinal tract is less active than that of the younger. Also liberation is slow, there is danger of accumulation of the drug after several days resulting in high blood levels and a delayed exaggerated response.

Multi Unit Particulate System offers several advantages such as

- Improve gastric absorption.
- Minimize local irritation.
- Offers high degree of flexibility.
- Reduces dose dumping.
- Reduces inter & intra subject variability.

1.4 MULTIPARTICULATES[9, 18, 19, 20]

Multiple unit dosage forms are essential where drug-excipients or drug-drug physicochemical interaction is possible in a single-unit formulation. They are also known to have less variance in transit time through the gastrointestinal tract than single-unit dosage forms. They are usually delivered in hard gelatin capsules or made into tablets that disintegrate instantly.

Types of Multiple unit dosage forms comprise

- Pellets
- Granules
- Mini tablets mini depots
- Micro particles (Microspheres or Microcapsules)
- Nano particles

1.5 PELLETS

Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration), obtained from diverse starting materials utilizing different processing techniques and conditions.

Desirable properties of pellets

Uncoated pellets:

- Uniform spherical shape and smooth surface
- Optimum size between 600 and 1000µm
- Improved flow characteristics
- High physical strength and integrity
- Good hardness and low friability

Coated pellets:

- High bulk density
- Ease and superior properties for coating
- Reproducible packing of beds and columns.
- Maintain all of the above properties.
- Contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits
- Have desired drug release characteristics

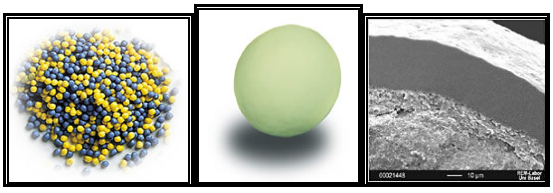


Figure 5 : (a) Pellets, (b) Perfect pellet, (c) Coated pellet

Advantages of pellets

- The smooth surface and the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch. Coating of pellets can be done with different drugs to enable a controlled release rate.
- In case of immediate release products, larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them.

- The beads or granules of different thickness of coatings are blended in the desired proportions to give the desired effect.
- The thickness of the coat on the pellets dictates the rate at which the drug or contents are released from the coated particles.
- By selecting the proper formulation, processing conditions and processing equipment, it is possible to attain smooth surfaced and uniform pellets.
- Improved appearance of the product and the core is pharmaceutically elegant.
- Pellets can be divided into desired dosage strength without process or formulation changes and also allows the combined delivery of two or more bioactive agents that may or may not be chemically compatible, at the same site or at different sites within the gastrointestinal tract.
- They offer high degree of flexibility in the design and development of oral dosage form like suspension, tablet and capsule.
- Recently, coated pellets are compressed to rapidly disintegrating tablets. For this purpose small pellets with the mean diameters below 0.5 mm are most suitable. Such pellets can be produced by direct pelletization methods.

Disadvantages of pellets

- The manufacturing of multiple unit dosage forms is more complicated and more expensive.
- The filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved**.**

1.5.1 Theory of pellet formation and growth[19]

- ❖ Nucleation
- ❖ Coalescence
- ❖ Layering
- ❖ Abrasion transfer

Theory of pellet formation can be explained as follows.

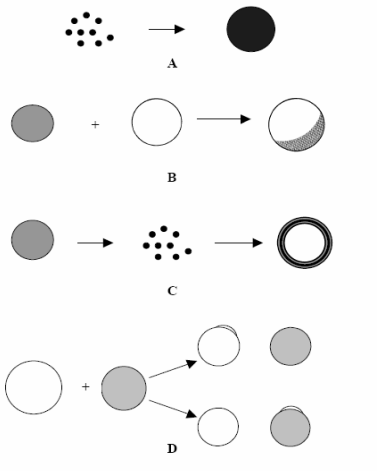


Fig 6: (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer

1.5.2 PELLETIZATION TECHNIQUES:

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. The type of coating technique strongly affects the film microstructure and thus affects the release mechanism and rate from pellets coated with polymer blends. There are several manufacturing techniques for production of spherical pellets.

The techniques involved are

1. Agitation
2. Compaction
3. Layering
4. Globulation

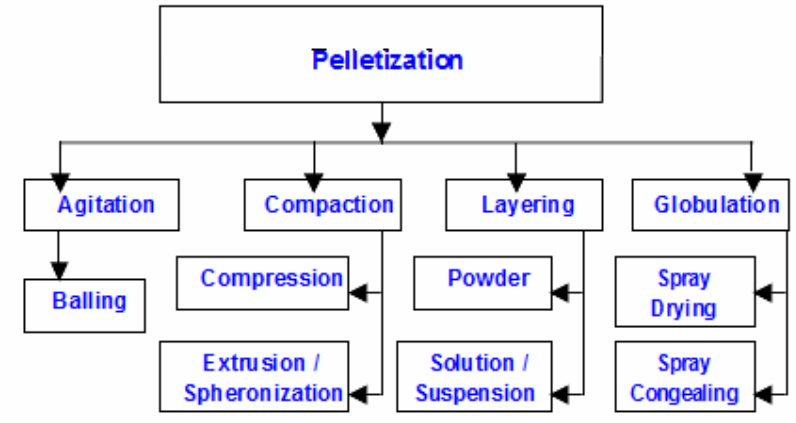


Fig 7: Different Pelletization Techniques

1.5.2.1. AGITATION:

a) Balling:

Finely divided particles are converted upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or tumbling motion. Pans, discs, drums, or mixers may be used to produce pellets by the balling.

1.5.2.2. COMPACTION:

a) Compression:

Mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size**.**

b) Extrusion – Spheronization:

It is a multistep process invented by Nakahara, in 1964, involves dry mixing of the active compound with excipients, granulation of wetted mass, extrusion of the mass, transfer of the mass to spheronizer to produce spherical shape, drying of the wetted mass in a dryer, and at the end screening to obtain required particle size.

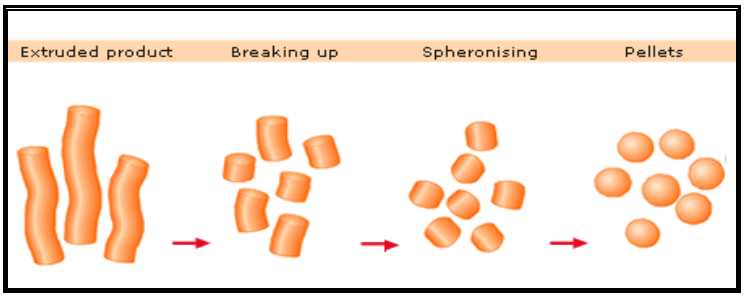


Figure 8: Principle of Extrusion – Spheronization process

1.5.2.3) LAYERING:

In this process, drug is layered onto seed materials (generally, a coarse material or nonpareil) in powder, solution or suspension form and leads to heterogeneous pellets, which consist of an inner core region and an outer shell region of a different composition. This process is classified into three categories namely

a. Direct pelletization,
b. Powder layering,
c. Solution or suspension layering

a) Direct pelletization

A process that leads to formation of homogeneous pellets which have microscopically uniform structure and no core can be detected. Direct pelletization is mainly performed in high shear mixers and fluidized bed equipment

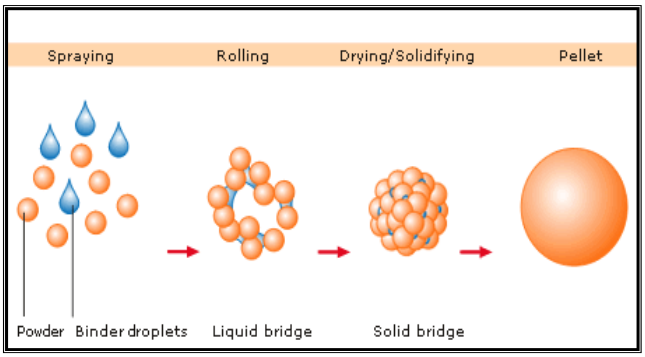


Figure 9: Principle of direct pelletization process

b) Powder Layering

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both, on preformed nuclei or cores with the help of a binding liquid.

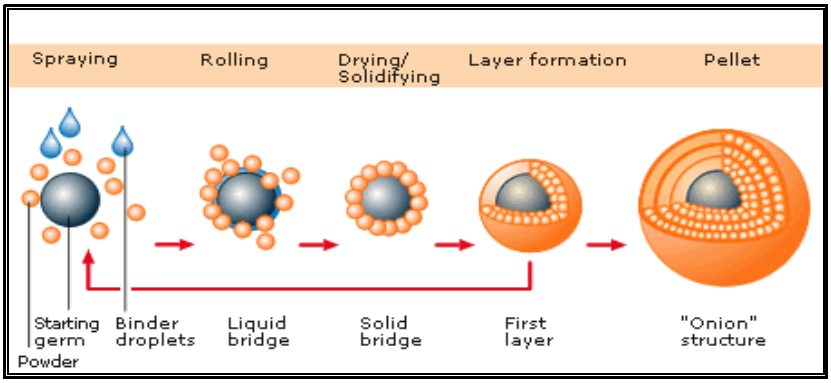


Figure 10: Principle of Powder layering process

Equipment used is tangential spray/centrifugal/rotary fluidized bed granulator. This technology is applied to produce sustained release Cyclobenzaprine Hydrochloride multiple unit pellets for improving the drug release in acidic media, due to the enhancement of the polymer film formation on the surface of the pellet.

Some of the disadvantages are:

- Low amount of drug loading which is not suitable for high-dose drugs
- Final composition of pellets can vary if spray loss occurs.

c) Solution/Suspension layering:

In the case of Solution/Suspension layering, growth of pellets involve deposition of successive layers of solution and/or suspension of drug substance and binders on existing nuclei, which may be inert seed, crystal or granule. The drug particles are dissolved or suspended in the binding liquid, with or without the binder. Droplets of the binding liquid spread on the surface of the nuclei.

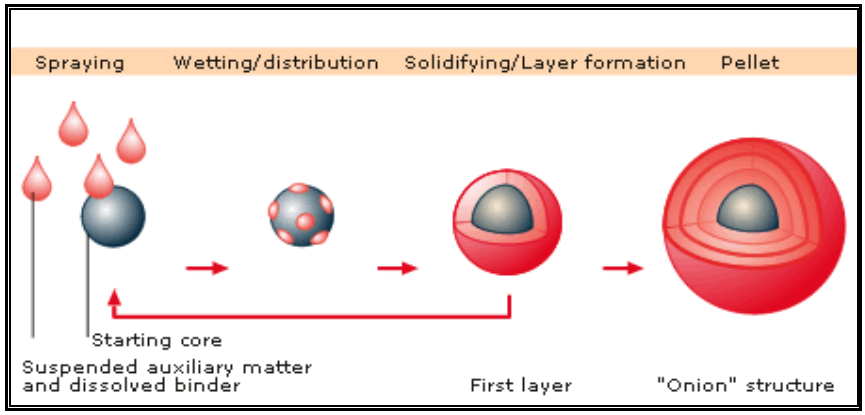


Figure 11: Principle of Solution/Suspension layering process

During drying, liquid evaporates and the dissolved substances crystallize out and capillary forces which are formed draw the particles towards each other and towards the inert seed, forming solid bridges. In suspension layering, particles have low solubility and are bonded by solid bridges formed from the hardening binder i.e., that higher concentration of binder might be necessary.

Suspension layering is usually used when the desired drug loading of the pellets is low because production of pellets from low solids content formulation is not economically feasible.

The most common configuration used is Wurster bottom spray coater.

1.5.2.4. GLOBULATION:

Globulation or droplet includes spray drying and spray congealing.

a) **Spray drying**: Drug entities in solution or in suspension form are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. It is generally employed to improve the dissolution rates and hence, bioavailability of poorly soluble drugs.

b) **Spray congealing**: A process in which a drug is allowed to melt, disperse, or dissolve in hot melts of gums, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide spherical congealed pellets under appropriate processing conditions.

1.5.3 COATING OF PELLETS:

The application of coating is usually based on one or more of the following:

- ❖ To mask the taste, odor or color of the drug.
- ❖ To provide physical and chemical protection to the drug.
- ❖ To control the release of the drug.
- ❖ To protect the drug from the gastric environment of the stomach with an acid resistant coating.
- ❖ To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.
- ❖ To provide pharmaceutical elegance by use of special color.

1.5.3.1 TYPES OF COATING:

a. Sugar coating

b. Film coating

c. Enteric coating

d. Extended release coating.

Sustained release coating is used in the present formulation. Commonly used sustained release polymers are

Ethyl cellulose, cellulose acetate, polyvinyl acetate, neutral copolymers based on ethyl acrylate & methyl acrylate, eudragit NE, RS or RS 30D, RL or RL 30D.

1.5.4. COATING EQUIPMENTS:

Most of the coating processes use one of three general types of equipments.

1. The conventional Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

1.5.4.1. Conventional Coating Pan:

In this technique the granules or sugar spheres are placed in the coating pan and the coating solution is sprayed on the granules by atomizer with pressure.

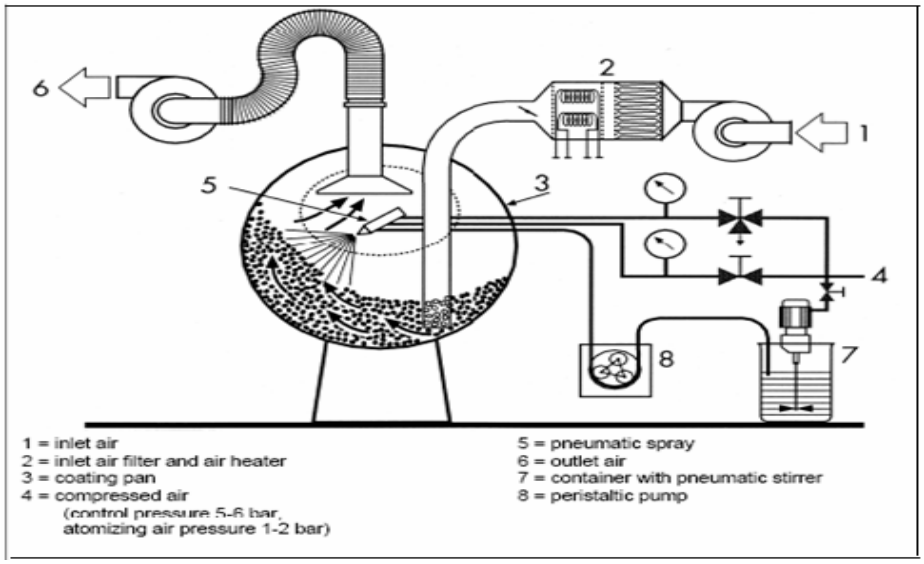


Fig 12 : Conventional Coating Pan

1.5.4.2. Perforated coating pan:

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 g to 1kg. This model efficiently carries out the following operations: Aqueous film coating of tablets/pellets; Non-aqueous organic solvent Based film coating of tablets/pellets; and Enteric Film coating of tablets/pellets. The basic units of the system are: Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor.

Figure 13: **NEOCOTA(Perforated pan)**

Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical air tight housing provided with a suitable door and frontglasswindow. This housing of pan with drive is a stainless steel Cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, ex-haust unit and an air fitter. Fig showing Neocota is an automatic coating system for tablets having a capacity of 500g to1kg. Aqueous film coating and non aqueous film coating is carried out in Neocota.

1.5.4.3. The Fluidized bed coater or Fluidized Bed Processor (FBP)[20]

The Fluid Bed Technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is as per GMP standards it is a closed system. The second advantage of the Fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine. There is considerable diversity in methods of using fluidized bed technology. For e.g. liquids can be applied to fluidized particles in a variety of ways, including top, bottom and tangential spraying.

Production of homogenous pellets is usually carried out in extruder spheronizer, high-shear mixer and rotary fluidized bed, while the production of heterogeneous pellets and particle coating is carried out in top spraying or different types of bottom spraying fluidized bed equipment.

A fluidized bed system is a unique process for uniform, continuous and coating of granulates, pellets and powders. Aqueous or organic coatings can be applied. Coating and drying takes place in one machine.

Principle of Operation:

In fluid bed processor, particles are fluidized and the coating fluid is sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.

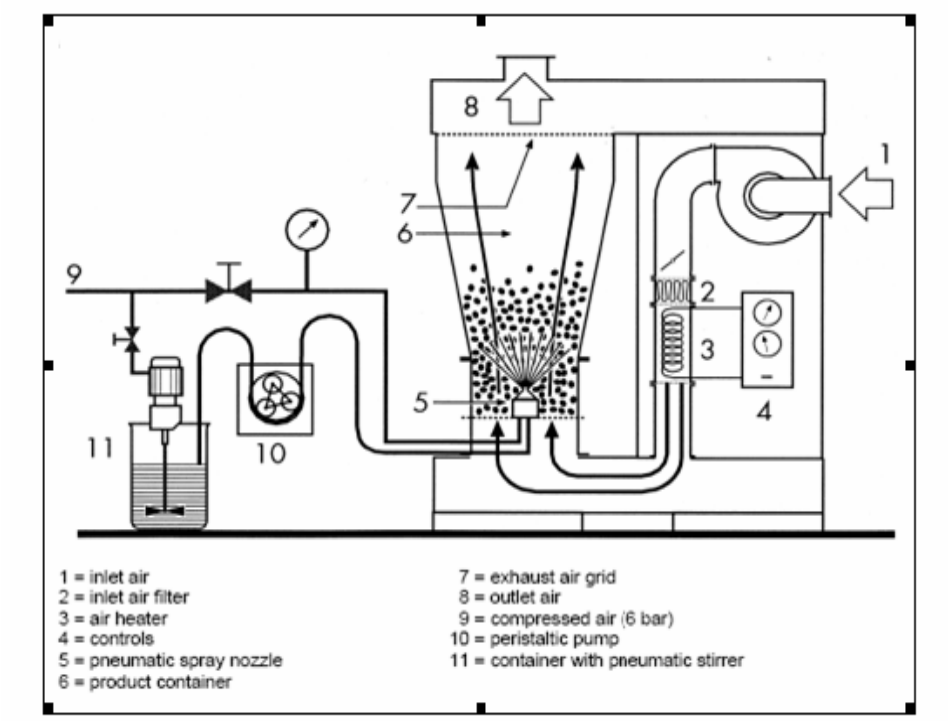


Figure 14: Fluidized Bed Processor

Advantages of Fluidized Bed Processor:

- All-in-one process from demanding powder coating to simple drying.
- Unique technology that combines outstanding spray behavior with optimum media delivery and easy cleaning.
- Simple handling for both horizontal and vertical product flow can be realized with all sizes.
- The unique ABC-technology (Anti-Bearding-Cap) allows spraying without bearding. The perfect supplement to the ABC-technology is the unique Nano-coating to the nozzle which prevents the deposit of coating material on the nozzle cap.
    - No process downtime due to cleaning of the nozzle
    - No blocked liquid inserts
    - No interference of spray pattern
- Process advantages are uniform, continuous product coating. Aqueous or organic coatings can be applied. Coating and drying take place in one machine.

1.5.4.3.1. Types of Fluid Bed Systems[20]

a) Top Spray (Granulator)

b) Bottom Spray (Wurster Coating)

c) Tangential Spray (Rotor Pellet Coating)

a) Granulator/Top-spray process → is preferred when a taste masking coating is being applied. Additionally it is suitable for the application of hot melt coating**.**

b) Wurster/Bottom spray process → is preferred for the application of modified-release coating to a wide variety of multi-particulates; also suitable for drug layering when the drug dose is in the low to medium rage.

In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle. Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate.

c) Rotor/ Tangential spray process → is suitable for the application of modified-release film coating to a wide range of multi-particulate products. It is ideal for drug layering when the dose is medium to high. It is also useful as a spheronizing process or producing spheres.

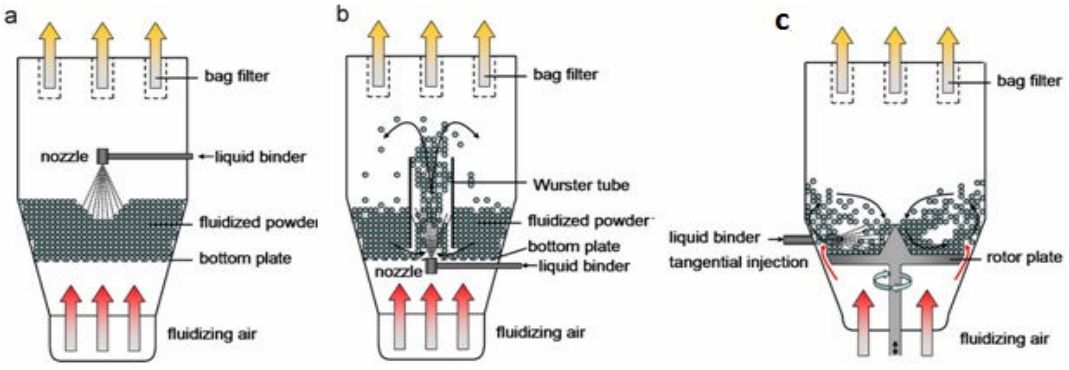


Fig 15 :(a) Principle of Bottom spray batch fluid coating. (b) Principle of Top-spray batch fluid coating. (c) Principle of Tangential spray batch fluid coating

1.5.5. Variables in FBP:

a. Formulation-related variables

b. Equipment-related variables

c. Process-related variables

Table No.2: Formulation Related Variables:

Variable	Effect
a) Primary Materials	Low particle density, a narrow particle size range, crystalline or amorphous nature, and wettability, a particle shape that approaches spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing are effective.
b) Binder(type, binder concentration and content)	Low friability, uniform flow, low bulk density, porosity, and size distribution are effective.
c) Solvent for Binder	The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of product being granulated.

Table No.3: Equipment-Related Variables:

Variable	Effect
a) Design	Difficulty in scaling up from the laboratory units in a linear scale due to different suppliers.
b) Air Distributor Plate	Identified by their percentage of open area. 3-40% of open area normally available. Small open area: large pressure drop, uniform fluidization.
c) Pressure Drop(_P)	A blower with an appropriate _P will fluidize the process material adequately.
d) Shaker and Blow-Back Cycle Mechanism	Bag filters with a blow-back or use of stainless steel filter bags in which air under pressure is pulsed through the filters.
e) Other equipment factors	Granulator bowl geometry, conical shape of the container and expansion chamber is preferred in which the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2.

Table No.4: Process related variables:

Process parameter	Effect
a) Inlet air temperature	Higher: finer granules. Lower: larger, stronger granules.
b) Humidity	Increase in humidity: larger granule size, longer drying times.
c) Fluidizing airflow	Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.
d) Nozzle and nozzle height	A binary nozzle produces finest droplets and is preferred. Optimum nozzle height should cover the bed surface. Too close to the bed: will wet the bed faster, producing larger granules. Too high position: creates finer granules, and increase granulation time.
e) Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size, and granule size. Higher liquid flow rate will produce larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.
f) Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.
g) Rotor Speed	Higher rotation rates resulted in excessive friability of the cores and loss of the coating powder.
h) Spray rate	Lower spray: longer processing time resulting in a lower porosity of the pellets. Higher spray: higher water content, shorter processing time and larger pellets, shorter time for liquid to evaporate, broader size distribution.
i) Moisture content	There is sensitive relation between moisture content and particle size, and moisture sensitivity depends strongly on the formulation, especially the fraction of pelletization aid.

1.5.6. Excipients for pellets:

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form. The excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations.

Table No.5: Examples of commonly used excipients

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch
Lubricant	Calcium stearate, glycerin, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
PH adjuster	Citrate, phosphate, meglumine
Surfactant	Polysorbate, Sodium lauryl sulphate
Glidant	Talc, starch, Magnesium stearate
Release modifier	Ethyl cellulose, carnauba wax, shellac

1.6. CAPSULES [21, 22]

Capsules are solid dosage forms in which the drug or a mixture of drugs is enclosed in hard or soft gelatin capsules. These shells made up of gelatin and this can be intended for oral administration.

These are available in various sizes, shapes and capacity.

1.6.1. TYPES OF CAPSULES

a) Hard gelatin capsules

b) Soft gelatin capsules

Both of these classes of capsules are made from aqueous solutions of gelling agents like, i) Animal protein mainly gelatin, ii) Plant polysaccharides or other derivatives like carragenans and modified forms of starch and cellulose.

Other ingredients can be added to the gelling agent solution like plasticizers such as glycerin and/or sorbitol to decrease the capsule's hardness, coloring agents, preservatives, disintegrants, lubricants and surface treatment.

a) Hard gelatin capsules

Which are normally used for dry, powdered ingredients or miniature pellets (also called spheroids that are made by the process of Extrusion and Spheronization) or tablets. These sizes are designed by in numbers.

Table No.6: Capsules sizes and their fill weights

S.No	Size of capsules	Volume in ml	Fill weight in mg
1	000	1.37	615-1370
2	00	0.95	430-950
3	0	0.68	305-680
4	1	0.50	225-500
5	2	0.37	165-370
6	3	0.30	135-300
7	4	0.21	95-210
8	5	0.13	60-130

b) Soft gelatin capsules

Which are primarily used for oils and for active ingredients that are dissolved or suspended in oil.These are classified depending upon the sizes and capacities.

The number represents capacities in minims

1) Round-1,2,3,4,,5,6,7,8,9,28,40,40T,80T and 90T.

2) val-1,2,3,4,,5,6, 7..5,10,12,16,20,40,60,80,85 and 110.

3) Obolong-3,4,5,6,8,9.5,11,14,16,20,90 and 360.

4) Tube-5,6,8,17.5,30A,30B,35,45,55,65,90,160,250,320 and 480.

5) Misc-6, 17, 30, 35, 60 and 80.

1.6.2. Capsules Standards and limits

a) Description

It should comply with specifications of product.

b) Content of active ingredients

Limit: 90 to110% of label claim or as per In house limit.

c) Uniformity of weight

Table No.7.

Average weight of capsules content	Percentage deviations allowed
less than 300mg	10%
300mg or more	7.5%

d) Disintegration test

i) Hard gelatin capsules

Disintegration time shall not be more than 30 min.

ii) Soft gelatin capsules

Disintegration time shall not be more than 60 min.

Table No.8: Standard length & locked length for hard gelatin capsules in mm

Size	Cap	Body	Locked length
000	12.80-12.95	22.10-22.20	26.4
00	11.74-11.86	20.12-20.25	23.3
0	10.68-11.68	18.22-19.22	21.7
1	9.51-10.51	16.22-17.22	19.4
2	8.67-9.67	14.84-15.84	18.0
3	7.73-8.73	12.98-13.98	15.9
4	6.97-7.97	11.84-12.84	11.1

1.7 SKELETAL MUSCLE RELAXANTS

1.7.1. HISTORY [23]

The earliest known use of muscle relaxant drugs dates back to the 16th century, when European explorers encountered natives of the Amazon Basin in South America using poison-tipped arrows that produced death by skeletal muscle paralysis. This poison, known today as curare, led to some of the earliest scientific studies in pharmacology. Its active ingredient, tubocurarine, as well as many synthetic derivatives, played a significant role in scientific experiments to determine the function of acetylcholine in neuromuscular transmission. By 1943, neuromuscular blocking drugs became established as muscle relaxants in the practice of anesthesia and surgery.

The U.S. Food and Drug Administration (FDA) approved the use of Cyclobenzaprine hydrochloride was approved on August 26, 1977

1.7.2. Muscle spasm:

Many diseases of the brain and spinal cord produce an increase in muscle tone (is sustained partial muscle contraction), which can be painful and disabling. Spasticity resulting from birth injury or cerebral vascular disease, and the paralysis produced by spinal cord lesions are examples. Local injury or inflammation, as in arthritis, can have the same effect, and chronic back pain is also often associated with local muscle spasm.

1.7.3. Skeletal muscle relaxants [24, 25]

A muscle relaxant is a drug which affects skeletal muscle function and decreases the muscle tone and / or cause paralysis. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. The term "muscle relaxant" is used to refer to two major therapeutic groups.

1. Neuromuscular blockers (or) peripherally acting muscle relaxants
2. Spasmolytics (or) centrally acting muscle relaxants

Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no CNS activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis. Spasmolytics, also known as "centrally-acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxant. The term is commonly used to refer to spasmolytics only.

1.7.3.1. CLASSIFICATION:

I.) PERIPHERALLY ACTING MUSCLE RELAXANTS:

1. NEUROMUSCULAR BLOCKING AGENTS:

A. Non depolarizing (competitive) blockers

1. Long acting :

d-tubocurarine,

pancuronium,

pipecuronium.

2. Intermediate acting:

Vecuronium,

Atracurium,

Cisatracurium,

Rapacuronium.

3. short acting:

Mivacurium.

B. Depolarizing blockers:

Succinyl choline,

Decamethonium.

2. DIRECTLY ACTING AGENTS:

Dantrolene sodium,

Quinine.

II.) CENTRALLY ACTING MUSCLE RELAXANTS:

I. mephenesin group

Mephenesin,

Methocarbamol,

Chlorzoxazone,

Chlormezanone.

II. Benzodiazepines

Diazepam,

Clonazepam,

Clobazam.

Cyclobenzaprine.

III. GABA Derivative

Baclofen

IV. Central α_2 agonist

tizanidine

I.) PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS: [26]

a) Neuromuscular blocking agents:

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of the skeletal muscle. These Neuro muscular blockers are structural analogs of acetylcholine, and either as antagonist (non depolarizing type) or agonists (depolarizing type) at the receptors end plate of the neuromuscular junction.

Neuro muscular blockers are clinically useful during surgery for produce complete muscle relaxation, without having to employ higher anaesthetic doses to achieve comparable muscle relaxation.

b) Directly acting agents:

The drug like Dantrolene which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum, and Baclofen, which acts at GABA receptors in the central nervous system.

II.) CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS [25]

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal post synaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Poly synaptic pathways in the ascending reticular formation which are in the maintenance of wakefulness are also depressed, through to a lesser extent. All centrally acting muscle relaxants do have some sedative property. They have no effect on neuromuscular transmission and on muscle fibres, but reduce deliberate rigidity, upper motor neurone spasticity and hyper reflexia.

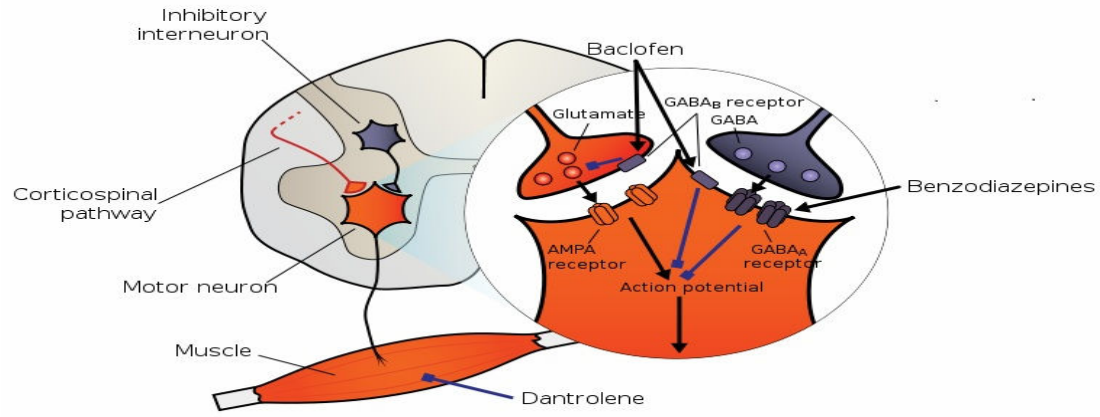


Fig.16 : Mechanism of action of centrally acting muscle relaxants.

A view of the spinal cord and skeletal muscle showing the action of various muscle relaxants. Black lines ending in arrow heads represent chemicals or actions that enhance the target of the lines. Blue lines ending in squares represent chemicals or actions that inhibition the target of the line.

The generation of the neuronal signals in motor neurons that cause muscle contractions are dependent on the balance of synaptic excitation and inhibition that the motor neuron receives. Spasmolytic agents generally work by either enhancing the level of inhibition, or reducing the level of excitation. Inhibition is enhanced by mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA.

2. Literature Review

2.1. Literature Review of Drug Delivery

Gangane PS *et al*.,(2008)[27] reported the preparation of cinnarazine pellets by powder-layering technique, using Cinnarizine as active ingredient and Eudragit RS-100, Eudragit RL-100, Ethyl cellulose as coating agent, with propylene glycol as plasticizers and PVPK-30 as binder. Pellets coated with 10% Eudragit RS-100 showed promising results releasing more than 95% of drug up to 12 hours. This study concluded that the powder layering technique can be used for designing sustained release drug delivery systems providing drug release over a period of 12 hours.

Crilles C. Larsen *et al.*, (2003)[28] reported the parameters with effect on maximum spray rate maximum relative outlet air humidity when coating pellets in a fluidized bed. The tested variables include type of water based modified release film coating (aqua coat ECD) coating principle (top spray, bottom spray) , inlet air humidity and type of pellets (sugar spheres, microcrystalline cellulose). The maximum spray rate was not influenced by the coating principles.

Simon Ensslin *et al*., (2008)[29] studied internal structure and drug release mechanism of modified release pellets coated with blends of poly vinyl acetate (PVAc) and poly vinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG). The highly soluble drug Chlorpheniramine maleate (CPM) was used as a model compound. A faster water influx into PVAc/PVA-PEG film coated pellets did not result in a fast drug release. Despite a fast drug solubilization within the pellets, drug release was initiated after 2 hrs, suggesting a one way stream of water during the observed lag-time.

Sreekhar cheboyina *et al*., (2008)[30] reported a novel freeze pellatization technique for the preparation of wax based sustained release matrix pellets for water-soluble drugs. The drug release significantly depended on the wax type used and the aqueous drug solubility. The drug release decreased as the hydrophobicity of wax increased. In glyceryl monostearate (GMS) pellets, drug release rate decreased as the loading of theophylline increased. On the contrary, the release rate increased as the drug loading of diltiazem HCl increased in precirol pellets.

Nantharat Pearnchob *et al*., (2003) [31]studied the powder layering technique with ethyl cellulose powder to achieve extended release. The film forming ability of ethyl cellulose powder and the effect of formulation factors (plasticizer type and concentration) and curing conditions (curing temperature and time) were investigated. The coating formulation was divided into two components consisting of a powder mixture (polymer plus talc) and a mixture of liquid materials (plasticizer plus binder solution), Propranolol hydrochloride was used as a model drug, Despite the high glass transition temperature of ethyl cellulose (133.4^0C), micronized ethyl cellulose powder can be used for dry powder coating by adjusting the coating temperature, amount and type of plasticizer applied, and curing conditions. 40% plasticizer and a curing step (80^0C, 24 h) were required to achieve complete coalescence of the polymer particles and extended drug release of coated pellets. Although ethyl cellulose-coated pellets had an uneven surface, extended drug release could be obtained with coating level of 15%.

Shajahan Abdul *et al.*, (2010)[32] studied a flexible technology, MUPS (multiple unit particulate system) for modified-release drugs. Oral modified –release multiple- unit dosage forms have always been over effective therapeutic alternative to conventional or immediate release single-unit dosage forms. The multi particulates are usually formulated into single unit dosage forms such as filling them into hard gelatin capsules or compressing them into tablets. These MUPS are expected to disintegrate rapidly into individual pellets and provide drug release profile similar to that obtained from uncoated pellets.

Caroline De sire e Kablitz *et al.*,(2008)[33] reported the dry coating process is an emerging coating technology using neither organic solvents nor water. In contrast to liquid-borne coatings, coating material application and film formation are divided into two phases, the coating phase where the powdery coating material is applied together with the liquid plasticizer, and the curing phase. In this study the coating phase was characterized with respect to the forces acting between the polymer particles during material application. HPMC was used as enteric resistant polymer, triethyl citrate (TEC), Myvacet (di acetylated mono glyceride) and a mixture of both as liquid additives. Inter particle forces were found to be similar when using TEC or a mixture of TEC and Myvacet_. In contrast, inter particle forces were higher when using solely Myvacet. This is attributed to the fact that Myvacet does not penetrate

into the polymer without TEC which is acting as a penetration enhancer. The highest inter particle force determined by AFM is in accordance to the highest coating efficiency which has been found for the corresponding coating formulation containing HPMC AS and Myvacet.

Kumar vikas *et al.*, (2011)[34] reported the pelletization technique with the advent of controlled release technology that the full impact of the inherent advantages of pellets over single unit dosage forms have been realized, not only has focused on the refining and optimizing pelletization techniques, but also focused on the novel approaches and procedures for manufacturing of pellets. The present review outlines the manufacturing and evaluation of pellets. There are various types of pellatization techniques like spheronization and extrusion, pelletization by powder layering, pelletization by solution layering &direct pelletization. The techniques namely extrusion and spheronization, hot melt extrusion cryo pellatization have been discussed along with parameters affecting pellatization.

Balasubramaniam J *et al*.,[35] reported the multi particulate pellets containing esomeprazole magnesium have been prepared using an extrusion spheronization process, employing povidone and crospovidone as non-traditional processing aids. Attempts have been made to prepare pellets of various sizes and ultimately investigate the levels of enteric coating that need to be applied in order to achieve a suitable delayed-release dissolution profile. While acceptable pellets, displaying appropriate drug delayed-release characteristics have been achieved, it is evident from this initial study that further formulation and processing refinements, with respect to the formation of the initial pellets, need to be made in order to create pellets with optimal sphericity characteristics and narrower particle size distributions.

Claudio Nastruzzi *et al*., (2000) studied the powder layering technique and also influence of formulation and process parameters on pellet production by pan technique. Here, in this study inert cores were intermittently treated with micronized drug powder and adhesive solution, which led to the formation of multiple layers of drug particles around and inert core resulting in the production of pellets that can be further coated by different polymers to obtain modified release formulations. Here in this study they used enteric polymer like acrylic polymer Eudragit L 30D and model drug as ibuprofen.

Singh S K *et al.*, (2009)[36] studied the development of delayed release micro pellet dosage form for Lansoprazole which is a benzimidazole anti ulcer agent. The approach of the present study was to make a comparative evaluation of polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulation of micro pellets were prepared using the fluid bed coater (FBC) with the air pressure 2.0 bar and the spray rate 10-15ml/min. Inlet temperature 60°C and bed temperature of 40°C is reliable for solution flow rate 10-15ml/min. Concerning results of prototype preparation of Lansoprazole the micro pellets were prepared using HPMC E5 polymer as release retardant in three different concentration i.e. 40%, 50%, 60% with three different concentration 8%, 10%, 12% of NaOH and Acrycoat L30D solution was used for enteric coating. Formulated micro pellets showed delayed *in vitro* dissolution behavior, probably due to optimized concentration of polymer.

Nicolas Follonier *et al.*, (1995)[37] studied the various ways of modulating the release of drug from hot melt extruded sustained release pellets prepared using polymeric materials. Diltiazem hydrochloride was used as a highly dosed, freely soluble model drug. Pellets obtained with this technique can be filled into hard gelatin capsules. To optimize the release profile of the drug the influence of different parameters, such as polymer type, addition of pore forming additives and hydrophilic polymers or size of pellets was studied. Swelling agents were included into the pellets , which reduces the burst release of drug.

Anette Pauli-Bruns *et.al*., (2010)[38] studied one-step preparation of sustained release matrix pellets, using a melting procedure in a fluidized bed apparatus, and tested in a full factorial design of experiments, using microcrystalline wax as lipophilic binder, theophylline as a model drug and talc as additional matrix forming agent. The three influence parameters were (A) size of binder particles, (B) fraction of theophylline in solid particles and (C) fraction of microcrystalline cellulose wax in formulation.

Rama Rao Nadendla *et al*.,(2011)[39] reported the design, characterization and *in vitro* evaluation of sustained release pellets of metoprolol succinate to reduce the dosing frequency employing pan coating technology. Initially metoprolol pellets were prepared by solution layering technology over non-pareil seeds employing pan

coating technology. Later, to sustain the release of drug over a period 20 hrs, secondary coating was given over the drug layered pellets using ethyl cellulose/ ethyl cellulose-hydroxy propyl cellulose were used to prepare different formulations. The *in vitro* dissolution studies revealed that the release rate is inversely proportional to percent of coating thickness. The mechanism of drug release follows Higuchi diffusion model.

2.2. Literature review of polymers

F. Siepmann *et al.,* (2009)[40] studied adjusting desired drug release patterns from ethyl cellulose coated dosage forms. Theophylline was used as model drug. Most important from a practical point of view, a broad spectrum of pH-independent drug release rates can easily be obtained from drug loaded pellets by simply varying the PVA-PEG graft copolymer content. An appropriate curing step after coating is required, but interestingly the investigated curing conditions (differing in time and relative humidity) resulted in very similar drug release patterns, indicating that stable film structures are likely to be achieved.

M.F. Saettone *et al.,* (1995)[41] studied the effect of different polymer plasticizer combinations on 'in-vitro' release of theophylline from coated pellets. This investigation evaluated the influence of different plasticizer/polymer combinations on theophylline (TH) release from pellets coated with latex aqueous dispersions of ethyl cellulose (EC) or acrylic polymers (ACR). For both types of coating, the drug release rate decreased with increasing plasticizer content. A correlation was found between the permeability coefficients (Pwv) to water vapour of free films, having the same composition as those used for coating, and drug release.

J.B. Dressman *et al.,* (1995)[42] reported the aqueous latex dispersions of ethyl cellulose are often used to form controlled release coatings on pharmaceutical dosage forms. These products exhibit pH dependent release characteristics, with release rates typically being slow in water and dilute acid solutions and faster in solutions buffered to pH values near neutral. The source of this pH dependant release is not obvious, since the principle mechanism of release is by osmotic pumping, the coating polymer is neutral and the effect is seen even with drugs that do not ionize within the pH range . In this research used phenyl propanolamine HCl pellets over coated with ethyl

cellulose to investigate the source of pH dependency of release. pH dependency of release was observed in all batches plasticized with dibutyl sebecate, tri ethyl citrate was used as the plasticizer, release was virtually independent of pH.

Anand kumar M *et al.*, (2011)[43] reported the development and optimization of oral extended release formulation for tamsulosin hydrochloride using a combination of ethyl cellulose N-50 and Eudragit L-100 as a coating material. Initially trials were done to optimize the drug loading on to sugar pellets for its uniformity of size and Assay, varying the concentration of HPMC E-5 as binder, Aerosil as lubricant and sodium starch glycollate as disintegrant. The optimal coating formulation was achieved with Eudragit L-100 9% of the weight of the drug loaded pellets and ethyl cellulose N-50 with 25% of the Eudragit L-100 content. The drug release from the optimized pellets was compared with the Innovator product ,It showed the similarity factor (F2) of **76.43.**

Fatemeh Sadeghi *et al.*, (2003)[44] studied the release of metoclopramide hydrochloride (a water-soluble cationic drug) and diclofenac sodium (a sparingly soluble anionic drug) from pellets coated with ethyl cellulose from aqueous ethyl cellulose dispersion (Surelease) at different coating loads was investigated. The release rates of each drug decreased as the coating load of Surelease increased. However, despite its lower water solubility, diclofenac sodium was released slightly faster than metoclopramide hydrochloride at equivalent coating loads. Differences between the release behaviour of the two drugs were probably due to an interaction between metoclopramide and the ammonium oleate present in the Surelease. The slower release of metoclopramide hydrochloride may be due to formation of a poorly soluble complex of the drug and the ammonium oleate. This complex, because of its large molecular size, may diffuse more slowly through the film, causing a reduction in the release rate of metoclopramide hydrochloride.

Cristoph Schmidt *et al.*, (2001)[45] reported the novel alternative to the incorporation into hard gelatin capsules or tablets, extended-release (Aquacoat- or Eudragit RS-coated) or enteric (Eudragit L-coated) pellets were embedded into congealed tablet-shaped PEG-plugs of different molecular weights, which rapidly released the pellets upon contact with aqueous fluids. The lower-molecular- weight PEGs (600 and 1000) were not suitable carrier materials: they dissolved the coatings

or significantly increased their permeability. The release characteristics of the original pellets were maintained after embedding the pellets into the higher-molecular-weight PEGs 4000 or 10,000. Aquacoat-coated pellets embedded in PEG 4000 exhibited a decreased drug release because of curing effects. Eudragit RS-coated pellets, stored at room temperature or above, showed an increased release.

Johan Hjartstam *et al.*, (1998)[46] reported the swelling behaviour of membrane-coated drug pellets . A coating membrane containing ethyl cellulose (EC) and hydroxy propyl methylcellulose (HPMC) in the range of 10–24% was used. By measuring the release rate of a drug during swelling experiments, it is possible to obtain an insight into the release mechanisms that are involved. The results revealed that the swelling of the membrane coat increased as the amount of HPMC increased. The expansion of the pellets continued until the release of the drug began, and also evaluated the swelling of pure EC:HPMC, where no change in volume occurred. It is believed that the swelling of the pellet coat is a result of water imbibition due to osmotic pressure.

Bernhard C Lippold *et al.*, (1999)[47] reported the release mechanisms of theophylline pellets coated with an aqueous ethyl cellulose (EC) dispersion containing plasticizers and hydroxy propyl methylcellulose (HPMC) as a water soluble pore former. Three different drug release mechanisms from coated pellets can be determined as a function of the water solubility of the plasticizers and the ionic strength of the release medium. Coated pellets with the addition of more hydrophilic plasticizers such as tri ethyl citrate (TEC) or diethyl phthalate (DEP) show an approximate zero-order-release rate. In contrast, two-phase release profiles can be observed from pellets coated with dispersions containing hardly soluble plasticizers such as di butyl phthalate (DBP) or di butyl sebacate (DBS).The drug diffuses through a hydrated swollen membrane containing EC, HPMC and insoluble plasticizer. The release mechanisms depend on the glass transition temperature of the ethyl cellulose and migration of the plasticizers and the pore former.

2.3. Literature review of drug

Jamunadhevi V. *et al.*, (2011)[48] reported the bilayer tablet of Cyclobenzaprine hydrochloride (CBH) and diclofenac potassium (DP) for the effective treatment of severe pain due to inflammation and muscle spasm. DP was formulated as immediate release layer and was prepared by wet granulation method

using purified water mixed with extra granular excipients. CBH was formulated as exteneded release layer using hydrophilic matrix (HPMC K100). The dissolution study of extended release layer showed that an increasing amount of HPMC results in reduced Cyclobenzaprine release.

Arnold J Weil, *et al.,*[49] reported the Diffucaps technology, the delivery system used for CER (Cyclobenzaprine Extended release), is a multi particulate bead system made up of multiple layers of drug, excipients, and release-controlling polymers. The beads can contain a layer of organic acid or alkaline buffer to control a drug's solubility by creating an optimal pH micro environment. Alternatively, Diffucaps beads can contain a solid solution of drug and crystallization inhibitor to enhance bio availability by maintaining the drug in its amorphous state. The Diffucaps beads contained in each CER capsule are made by coating an inert core (such as sugar) with a layer of the active drug, Cyclobenzaprine, and then by applying a sealcoat and rate-controlling membrane. The beads are small, approximately 1mm or less in diameter, and individual capsule shells are filled with sufficient quantity of these to yield a 15- or 30-mg dose of CER.

T. Farrell, Ph.D. *et al.*, (2007)[50] reported the Development of a Common Cyclobenzaprine Formulation for Both Encapsulation and Tabletting Using Star Cap 1500. The combination of star cap 1500/MCC is suitable to provide good compactibility characteristic to the formula and fast disintegration/dissolution to the film coated tablets. The satisfactory content uniformity of the capsules and tablets was achieved as a result of the excellent flow properties of the final blend and minimum potential segregation of the active ingredients during process. The *in-vitro* performance of capsules and film coated tablets has been proved similar with a complete release in the first 15 minutes of the dissolution profiles.

3. DRUG & EXCIPIENTS PROFILE

3.1. DRUG PROFILE

CYCLOBENZAPRINE HYDROCHLORIDE[51-57]

3.1.1. Introduction:

Cyclobenzaprine hydrochloride is a newer centrally acting skeletal muscle relaxant for oral administration and it is used for the relief of muscle spasm associated with acute, painful musculoskeletal conditions.

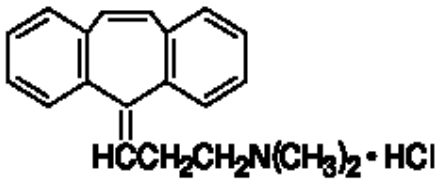
Synonym : Cyclobenzaprine hydrochloride

Chemical Name :

Dimethyl(3-{tricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3(8),4,6,9,12,14-heptaen-2-ylidene}propyl)amine

Molecular formula : $C_{20}H_{21}N.HCL$

Structure:



Structure of Cyclobenzaprine Hydrochloride

Molecular weight : 311.9 g/mol.

CAS number : **305-53-7**

Brand names : Bonelax®, Amrix®.

Biopharmaceutical classification system:

According to the BCS classification it belongs to Class - III

Pka value : 8.47

Category **:** Skeletal muscle relaxant (central)

Anti depressant agent (Tricyclic)

Tranquilizing agent,

Anti fibromyalgia agent.

Legal status **:** Rx Prescription only

3.1.2. PHYSICO CHEMICAL PROFILE:

Description:

White crystalline odorless amine salt.

Solubility:

Freely soluble in water & alcohol,

Sparingly soluble in isopropanol,

Insoluble in hydrocarbon solvents.

Melting point:

By capillary method melts at 217 ^{0}C (Melts between 215 to 219 ^{0}C)

3.1.3. PHARMACEUTICAL PROFILE:

Dosage **:** 15&30 mg capsules SR (Bonelax, Amrix),

5&10 mg tablets (Flexeril),

7.5 mg tablet (Fexmid) .

3.1.4. ANALYTICAL PROFILE:

UV spectrophotometry: [57]

Determination of Cyclobenzaprine hydrochloride in its pure and in capsule dosage forms using spectrophotometric method in Ultraviolet region was reported. Cyclobenzaprine hydrochloride exhibits maximum absorption maxima at 290 nm in 0.1N HCL.

3.1.5. PHARMACOLOGICAL PROFILE:

Mechanism of action:

Cyclobenzaprine is a skeletal muscle relaxant which relieves muscle spasm of local origin (that is, problems originating in the muscle itself and not in the nerves controlling the muscles) without interfering with muscle function. It does not directly act on the neuromuscular junction or the muscle but relieves muscle spasms through a central action, possibly at the brain stem level. Cyclobenzaprine binds to the serotonin receptor and is considered a 5-HT2 receptor antagonist that reduces muscle tone by decreasing the activity of descending serotonergic neurons. Like other tri cyclic anti depressants, Cyclobenzaprine exhibits anticholinergic activity, potentiation of nor epinephrine, and antagonism of reserpine.

Cyclobenzaprine activates the locus cerelus in the brain stem leading to an increased release of nor epinephrine in the ventral horn of the spinal cord & subsequent inhibitory action of nor epinephrine on alpha motor neurons.

Cyclobenzaprine has been considered structurally related to the first generation Tricyclic antidepressants. Such Tricyclics including amitriptyline act to inhibit the uptake of nor epinephrine, resulting in increased trans synaptic or epinephrine concentration. They have been shown to exert analgesic effect in chronic nerve & muscle pain. Cyclobenzaprine may have a similar effect.

Pharmacokinetic properties:

Biological Half life : 8 – 18 hours.

Absorption:

Slowly but well absorbed after oral administration.

Immediate release (IR):

Mean oral bioavailability ranges from 33% to 55%. Reaches steady state in approximately 3 to 4 days following 3 times a daily dosing. C_{max} is approximately 80 to 319 ng/ml.

Extended release (ER):

T_{max} is 7 to 8 hours.

C_{max} is 8 to 20 ng/ml.

AUC is 354 to 780 ng.h/ml.

Distribution:

Highly bound to plasma proteins (93%).

Metabolism:

Extensively metabolized, primarily to glucuronide like conjugates (hepatic & intestinal).

Elimination:

IR:

Excreted primarily via kidneys. The $t_{1/2}$ is approximately 8 to 37 hours.

ER:

The $t_{1/2}$ is approximately 33 hours.

Clearance:

0.7L/min.

Pharmacodynamics:

Cyclobenzaprine, closely related to the anti depressant amitriptyline, is used as a skeletal muscle relaxant to reproduce pain and tenderness and improve mobility, unlike dantrolene. Cyclobenzaprine cannot be used to treat muscle spasm secondary to cerebral or spinal cord disease.

Like other Tricyclic antidepressants, Cyclobenzaprine exhibits anti-cholinergic activity, potentiation of nor epinephrine, and antagonism of reserpine.

Drug interactions:

Cyclobenzaprine hydrochloride extended-release capsules may have life-threatening interactions with MAO inhibitors. Cyclobenzaprine hydrochloride extended-release capsules may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

Therapeutic use:

Cyclobenzaprine hydrochloride is most commonly used as skeletal muscle relaxant (central acting) for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Dosage & administration:

Cyclobenzaprine HCl supplied as 15mg and 30mg capsules for oral administration. The recommended initial dose of the drug is one (1) 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) 30 mg capsule taken once daily or as two (2) 15 mg capsules taken once daily. It is recommended that doses be taken at approximately the same time each day.

Indications:

Cyclobenzaprine hydrochloride extended-release capsules is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle

spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

Cyclobenzaprine hydrochloride extended-release capsules should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine hydrochloride extended-release capsules have not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

Over dose:

Although rare deaths may occur from over dosage with Cyclobenzaprine HCl. Multiple drug ingestion (including alcohol) is common in deliberate Cyclobenzaprine overdose. As management of over dose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity may develop rapidly after Cyclobenzaprine overdose, therefore, hospital monitoring is required as soon as possible. The acute oral LD50 of Cyclobenzaprine HCl is approximately 338 and 425 mg/kg in mice and rats, respectively.

Overdose symptoms:

The most common effects associated with Cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome

Adverse effects:

Among the most common side effects of Cyclobenzaprine are drowsiness (which occurs in between 1 in 6 and 1 in 3 persons), dry mouth (between 1 in 14 and 1 in 4), and dizziness (between 1 in 30 and 1 in 9). Other reported side effects, for which the incidence is less than 1 in 30, include nausea, tiredness, constipation, blurred vision, unpleasant taste, nervousness, confusion, and abdominal pain or discomfort.

Pregnancy

Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy if the physician feels that it is necessary.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because Cyclobenzaprine is closely related to the Tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when Cyclobenzaprine hydrochloride extended-release capsules are administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Cyclobenzaprine hydrochloride extended-release capsules has not been studied in pediatric patients.

3.2 POLYMER PROFILE

3.2.1. ETHYL CELLULOSE N-50 [58, 59]

Non proprietary names :

BP : Ethyl cellulose

USP NF : Ethyl cellulose

Ph Eur : Ethyl cellulosum

Synonyms:

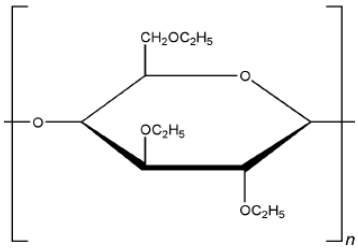
Aqua coat ECD; Aqualon; E 462; Ethocel; Surelease.

Chemical Name and CAS Registry Number:

Cellulose ethyl ether, [9004-57-3]

Empirical formula: $C_{12}H_{23}O_6 (C_{12}H_{22}O_5)_n C_{12}H_{23}O_5$

Structural formula:



Description:

A tasteless free flowing white to light tan colored powder.

Functional Categories:

Coating agent; flavouring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Incompatibilities:

Incompatible with paraffin wax and microcrystalline wax.

Solubility :

Insoluble in water, glycerin and propylene glycol but insoluble in varying degrees in certain organic solvents, depending upon the ethoxyl content. The addition of 10-20% of a lower aliphatic alcohol to solvents such as ketones, esters and hydrocarbons can improve the solubility.

Stability and storage condition:

It is resistant to alkalis both dilute and concentrated and to salt solutions. It is more sensitive to acidic materials than are cellulose esters. However the material can withstand dilute acids for a limited period of exposer. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by use of an antioxidant and a compound with light absorption properties between 230-340 nm. Ethyl cellulose should be stored between 7^0C and 32^0C in a dry area away from all sources of heat. Store in a well closed container.

Types: [35]

Ethyl cellulose is available as four ethoxyl types depends on ethoxyl content. Each of these ethoxyl types is subdivided into viscosity types. The viscosity designation indicates the nominal viscosity in centipoises for a 5% weight concentration in the standard viscosity solvent (5% ethyl cellulose in 80% toluene: 20% ethanol by weight).

Type	**Ethoxyl Content**
K-Type	45.0-47.2
N-Type	48.0-49.5
T-Type	49.6-51.5
X-Type	50.5-52.5

Grade	Viscosity Range, cps
N-7	5.6-8.0
N-10	8.0-11.0
N-14	12.0-16.0
N-22	18.0-24.0
N-50	40.0–52.0
N-100	80.0–105.0

Applications in Pharmaceutical Formulation:

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethyl cellulose in oral formulations is as hydrophobic coatings are used to modify the release of a drug, mask the taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation.

Ethyl cellulose dissolved in an organic solvent or solvent mixture, can, be used on its own to produce water insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films. Ethyl cellulose films may be modified to alter their solubility, by the addition hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethyl cellulose such as aquacoat ECD (FMC biopolymer) or surelease (colorcon) may also be used to produce ethyl cellulose films without the need for organic solvents.

Drug release through ethyl cellulose-coated dosage forms can be a slow process unless a large surface area (e.g. Pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. Studies have also suggested ethyl cellulose for use in floating micro particles based on low density foam powder, for gastro retentive drug delivery systems.

Use	Concentration
Microencapsulation	10.0-20.0
Sustained-release coating	3.0-20.0
Tablet coating	1.0-3.0
Tablet granulation	1.0-3.0

3.2.4. HYPROMELLOSE (HPMC) [62]

Non-proprietary Names

BP : Hypromellose

JP : Hydroxypropylmethylcellulose

PhEur : Hypromellosum

USP : Hypromellose

Synonyms

Benecel MHPC; E464; hydroxy propyl methyl cellulose; HPMC; Methocel; methylcellulose propylene glycol ether; Methyl hydroxy propyl cellulose; Metolose; Tylopur.

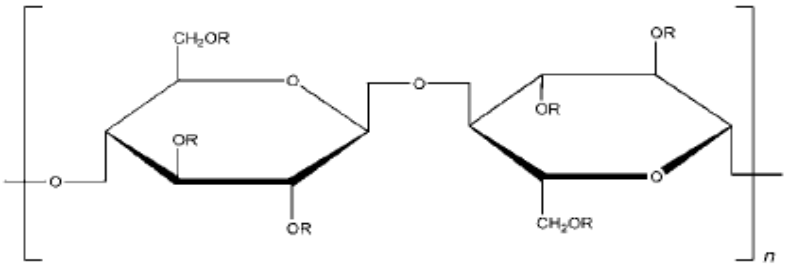
Chemical Name and CAS Registry Number

Cellulose hydroxy propyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight

O methylated and O-(2-hydroxypropylated) cellulose, 10000 – 150000

Structural Formula



Where R is H, CH_3, or CH_3CH (OH) CH2

Functional Category

Coating agent, film former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Description

Hypromellose is an odorless and tasteless, white or creamy- white fibrous or granular powder.

Melting point

Browns at 190–2008C; chars at 225–230^{0}C.

Glass transition temperature is 170–180^{0}C.

Solubility

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is non-ionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90^{0}C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an anti microbial preservative. When hypromellose is used as viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20^{0}C.

Methocel product	**Nominal viscosity** (mPas)

Methocel K100 Premium LVEP	100
Methocel K4M Premium	4000
Methocel K15M Premium	15 000
Methocel K100M Premium	100 000
Methocel E4M Premium	4000
Methocel F50 Premium	50
Methocel E10M Premium CR	10 000
Methocel E3 Premium LV	3
Methocel E5 Premium LV	5
Methocel E6 Premium LV	6
Methocel E15 Premium LV	15
Methocel E50 Premium LV	50

Applications in pharmaceutical Formulation

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, film coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as binder in either wet or dry granulation process. High-viscosity grades may be used to retard the drug release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solution to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. In addition, hypromellose is used is used in the manufacture of capsules, as wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

3.3 EXCIPIENTS PROFILE

3.3.1. POLYVINYL PYRROLIDINE (PVP K-30) [60]

Nonproprietary names:

BP : Povidone

JP : Povidone

Ph Eur : Povidonum

USP : Povidone

Synonyms :

E 1201; kollidon; plasdone; polyvidone; polyvinylpyrrolidine; PVP

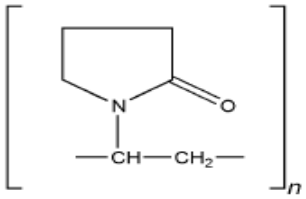
Chemical name and CAS registry number:

1-Ethenyl-2-pyrrolidinone homopolymer, [9003-39-8]

Empirical Formula:

$(C_6H_9NO)n$

Structural Formula:



Molecular Weight : 2,500 to 300,000

Types:

PVP is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value in the range 10-120.

Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	10 00 000
120	30 00 000

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occurs as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Functional Category:

Disintegrant; dissolution aid; suspending agent; tablet binder

Melting point:

Softens at 150^0C

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water. Practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Stability and storage condition:

Povidone darkens to some extent on heating at 150^0C with a reduction in water solubility. It is stable to a short cycle of heat exposure around 110-130^0C. Steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and hence require suitable preservatives.

Povidone can be stored under ordinary conditions without undergoing decomposition or degradation. However since the powder is hygroscopic, it should be stored in an air tight container in a cool, dry place.

Incompatibilities:

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin, and other compounds. The efficacy of some preservatives e.g. thiomerosal, may be adversely affected by the formation of complexs with povidone.

Applications in Pharmaceutical Formulation:

Povidone is used in the form of a solution as a binder in tablet granulations. It is also added to powder blends in dry form and granulated insitu by the addition of water, alcohol, or water-alcohol.

Use	**Concentration (%)**
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

3.3.2. POLY ETHYLENE GLYCOL-6000 [61]

Non proprietary Name

BP : Macrogols
JP : Macrogol 6000
PhEur : Macrogola
USP NF : Polyethylene glycol

Synonyms

Carbo wax; Carbo wax sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxy ethylene glycol.

Chemical Name and CAS Registry Number

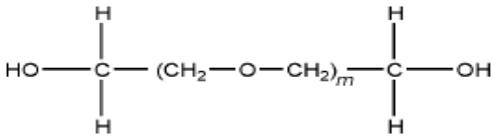
ά- Hydro-ω-Hydroxypoly-(oxy-1,2-ethanediyl), [25322-68-3]

Empirical formula

$HOCH_2 (CH_2OCH_2)_n CH_2OH$

n=3 for PEG-6000

Structural formula



Molecular weight : 7300-9300 (JP)

Functional category :

USP- Suppository base, solvent, tablet and/or capsule lubricant, ointment base.

BP - pharmaceutical aid.

Description:

Poly ethylene glycol as being an addition polymer of ethylene oxide and water. Poly ethylene grades 200-600 are liquids, 1000 and above are solids at ambient temperatures.

Liquid PEGs (PEG 200-600)

Clear, colorless or slightly yellow-colored, viscous liquids. The odor is slight but characteristic and the taste is bitter and slightly burning taste. PEG 600 can be solid at ambient temperatures.

Solid PEGs (PEG >1000)

The solid grades are white or off white in color and range in consistency between pastes and waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

Melting point:

PEG -6000: 55-63^{0}C

Solubility:

All grades are soluble in water and miscible in all proportions with other PEGs (after melting if necessary). Aqueous solutions of higher molecular weight grades may form gels.

Liquid PEGs are soluble in alcohols, glycols, acetone, glycerin and benzene.

Solid PEGs are soluble in methanol, ethanol(95%), acetone and dichloromethane. They are slightly soluble in ether and aliphatic hydrocarbons but insoluble in liquid paraffin, fats, mineral and fixed oils.

Stability and storage conditions

Chemically stable in air and in solution. PEGs do not support microbial growth nor become rancid. Stainless steel, aluminum, glass or lined steel are preferred for storage of liquid and low molecular weight products. Moisture may be absorbed especially the grades of molecular weight less than 2000. These must be stored in well-closed containers. Aqueous solutions of PEGs can be sterilized by autoclaving or filtration. Sterilization of solid grades by heat at 150^{0}C for 1 hr may induce oxidation darkening and the formulation of acidic degradation products.

Oxidation may occur if PEGs are exposed for long periods to temperatures exceeding 50^{0}C. Storage under nitrogen will reduce the possibility of oxidation.

Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by auto oxidation. Liquid and solid grades are incompatible with FD&C Red No.3 and Yellow No.5. Additionally the solid interact with FD&C Blue No.1 and Red No.1, 2&4 reactions occurs with lakes of the above dyes.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenol formaldehyde, polyvinylchloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

Applications in Pharmaceutical Formulation

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75^{0}C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

3.3.3. SUGAR SPHERES [63]

Nonproprietary names

BP : Sugar spheres

PhEur : Sacchari sphere

USP NF : Sugar spheres

Synonyms:

Non pareil, NPTAB, Nu-Core, Non-pareil seeds, PG sugar seeds, Sugar seeds, Nu-pariel PG, Suglets.

Description:

The USPNF 23 describes sugar spheres as approximately spherical granules of a labelled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. The diameter of sugar spheres varies from 200 to 2000 mm.

Particle size distribution:

Sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):

45–60 mesh (250–355 mm)	25–30 mesh (610–710 mm)
40–50 mesh (300–425 mm)	20–25 mesh (710–850 mm)
35–45 mesh (355–500 mm)	18–20 mesh (850–1000 mm)
35–40 mesh (420–500 mm)	16–20 mesh (850–1180 mm)
30–35 mesh (500–600 mm)	14–18 mesh (1000–1400 mm)

Functional categories:

Tablet and Capsule diluent.

Solubility:

Solubility in water varies according to the sucrose to starch ratio. The sucrose component is freely soluble in water, where as the starch component is practically insoluble in cold water

Stability and storage conditions:

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

Method of manufacture:

Sugar spheres are prepared from crystalline sucrose, which is cored using sugar syrup and a starch dusting powder.

Applications:

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multi particulate sustained release formulations. They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

It is used as a starting core for drug loading on pellets.

3.3.4. SUCROSE[64]

Non proprietary names:

IP	:	Sucrose
JP	:	Sucrose
PhEur	:	Saccharum
USP NF	:	Sucrose

Synonym:

Beet sugar, Cane sugar, refined sugar, saccharose, sugar

Chemical name and CAS Registry number:

β -D-fructofuranosyl- α -D-glucopyranoside [57-50-1]

Empirical formula and molecular formula: $C_{12}H_{22}O_{11}$, 342.30

Functional category

Base for medicated confectionery; coating agent; granulating agent; sugar coating adjunct; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; viscosity-increasing agent.

Description

Sucrose is a sugar obtained from sugar cane (saccharum officinarum), sugar beet (Beta vulgaris), and other sources. It contains no added substances. Sucrose occurs as colourless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odourless and has a sweet taste.

Melting point:

160-186^{0}C (with decomposition)

Stability and storage conditions

Sucrose has good stability at room temperature and at moderate relative humidity .It absorbs up to 1% moisture, which is released up to heating up to 90^{0}C.Sucrose caramelizes when heated to temperatures above 160^{0}C

Incompatibilities

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients e.g. ascorbic acid.

Applications in pharmaceutical formulations

Sucrose is widely used in pharmaceutical preparations syrup containing 50 - 67% sucrose is used in tabletting as a binding agent for wet granulation in the powdered form, sucrose serves as a dry binder (2–20% w/w)or as a bulking agent and sweetener in chewable tablets and lozenges. Sucrose syrups are also widely used as vehicles in oral liquid dosage forms to enhance palatability or to increase viscosity.

Use	**Concentration (% w/w)**
Syrup for oral liquid formulations	67
Sweetening agent	67
Tablet binder (dry granulation)	2–20
Tablet binder (wet granulation)	50–67
Tablet coating (syrup)	50–67

3.3.5. COLLOIDAL SILICONE DIOXIDE (Aerosil) [65]

Nonproprietary Names

BP : Colloidal anhydrous silica

PhEur : Silica colloidalis anhydrica

USPNF : Colloidal silicon dioxide

Synonyms

Aerosol; Cab – O – Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid: silicle; silicic anhydride; silicon dioxide fumed; wacker HDK.

Chemical Name & CAS Registry number

Silica [7631-86-9]

Empirical formula : SiO_2

Structural Formula : $SI0_2$

Molecular Weight : 60.08

Functional Category:

Adsorbent; anti caking agent; glidant; suspending agent; tablet disintegrant; viscosity – increasing agent, thermal stabilizer

Description:

Colloidal silicon dioxide is a sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white colored, odourless, tasteless, non gritty amorphous powder.

Stability and storage conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system.

However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be store in a well-closed container.

Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

Incompatibilities:

Incompatible with diethylstilbestrol preparations.

Solubility:

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Applications in Pharmaceutical formulation of Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products. Its small particle size and large specific surface area give it desirable flow characteristics which are exploited to improve the flow properties of dry powders in a number of processes, e.g. tableting.

Colloidal silicon dioxide is also used to stabilize emulsion and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of same refractive index transparent feels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity in largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

Use	**Concentration (%)**
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–0.5
Suspending and thickening agent	2.0–10.0

3.3.6. TALC: [66]

Non proprietary names:

BP : Purified talc

JP : Talc

PhEur : Talcum

USP : Talc

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name and CAS Registry Number:

Talc [14807-96-6]

Empirical formula:

$Mg_6 (Si_2O_5)_4(OH)_4$

Functional Category:

Anti caking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Description:

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Stability and storage conditions

Talc is a stable material and may be sterilized by heating at160^0C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds.

Moisture content

Absorbs insignificant amounts of water at 25^0C and relative humidities up to about 90%

Particle size distribution

Varies with the source and grade of material. Two typical grades are ≥99% through a 74 µm (#200mesh) or ≥99% through a 44 µm (#325 mesh).

Solubility

Practically insoluble in dilute acids and alkalies, organic solvents, and water.

Melting range

17-150^0C (commercial samples)

126-130^0C (highly pure)

Applications

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, although today it is less commonly used. However it is widely Used as a dissolution retardant in the development of controlled release products, also used as a lubricant in tablet formulations, in a novel powder coating for extended-release pellets, and as an adsorbent.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material, it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

Use	**Concentration (%)**
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluents	5.0–30.0

3.4. SOLVENTS PROFILE

3.4.1. Isopropyl alcohol [67]

Non proprietary Name:

BP : Isopropyl alcohol

JP : Isopropanol

PhEur : Alcohol isopropylicus

USP : Isopropyl alcohol

Synonyms:

Isopropanol, alcohol Isopropylieum, petrohol, dimethylcarbinol, 2-propanol, IPA,

Chemical Name and CAS Registry Number:

Propran-2-ol [67-63-0]

Empirical formula **:** C_3H_8O

Molecular weight **:** 60.1g

Melting point **:** 88.5^0C

Functional Categories:

Solvent, disinfectant.

Description:

Isopropyl alcohol is a clear, colourless, mobile, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Stability and storage condition:

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Solubility:

Miscible with benzene, chloroform, ethanol (95%) ether, glycerine, and water. Soluble in acetone. Insoluble in salt solutions. Forms an azeotrope with water containing 87.4% w/w isopropyl alcohol (boiling point 80.37^0C).

Incompatibilities:

Oxidizing agents like hydrogen peroxide and nitric acid decompose isopropyl alcohol. It may be slated out form aqueous mixtures by the addition of sodium chloride, sodium sulfate and other salts or by sodium hydroxide.

Applications in Pharmaceutical Formulation:

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations. It is used in lotions the marked degreasing properties may limit its usefulness in preparations used repeatedly. It is also used as a solvent both for tablet film-coating and for tablet granulation. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

4. AIM & OBJECTIVE OF THE WORK

AIM :

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle agent used in the relief of muscle spasm associated with acute, painful musculoskeletal conditions, as tranquilizing agent and as anti depressant.

The oral bioavailability of Cyclobenzaprine hydrochloride is 33-55%**.** In normal course of Therapy drug administration is required every 3-6hrs, thus warrants the use of sustained Release formulation for prolong action and to improve patient compliance.

Thus the aim of the present study was to develop a sustained release formulation of Cyclobenzaprine hydrochloride pellets using powder layering technique. The drug release profile of the test product was to mapped against innovator product.

The concept of drug delivery has been explored for the delivery of drugs for prolonged period of time for the past few years. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs. Utilizing the concept of incorporating drug into the polymer matrices and extend the drug release for prolong period of time, an attempt was made to design and evaluate sustained release pellets of Cyclobenzaprine hydrochloride.

The Object of the present work was:

- To formulate a drug delivery system, which provided a sustained release of the drug that maintained the plasma drug concentration above the MEC for an extended period of 16 hours.
- The dosing frequency was reduced by formulate into single capsule per day.
- Even though in market Cyclobenzaprine hydrochloride tablets were available, this work was objected to formulate pellets because of pellets are having good flow properties and high degree of flexibility in the design and development of formulation.
- Finally to provide the sustained drug delivery system which increases the patient compliance, effectiveness of therapy, reduces the chances of adverse effect and hyper sensitivity of reaction by maintaining the plasma drug concentration at the same level with in therapeutic range for the required period of time.

5. PLAN OF WORK

The following experimental protocol was designed to allow a systemic approach to the study

1. Innovator product characterization.
2. Preparation of calibration curve of Cyclobenzaprine Hydrochloride in 0.1N HCl
3. Determination of λ_{max} of Cyclobenzaprine Hydrochloride
4. Preformulation studies.
    a) Physical Appearance
    b) Solubility Studies
    c) Melting Point
    d) Physical Properties
5. Compatibility study of drug with excipients.
6. Formulation of sustained release Cyclobenzaprine HCl pellets.
7. Filling of drug pellets into capsules size no.4.
8. Evaluation of capsules
    a) Weight variation test.
    b) Friability test.
    c) Locking length test.
    d) Disintegration test.
    e) Moisture content test
    f) Assay.
    g) *In-vitro* drug release studies.
    h) Scanning Electron Microscopy (SEM) Of Optimized formulation.
9. Comparison of the formulations with reference.
10. *In-vitro* Release Kinetic models.
11. Accelerated Stability study of optimized formulation.

6. MATERIALS AND METHODS

6.1. MATERIALS USED:

Table No. 9: LIST OF CHEMICALS USED WITH THEIR SUPPLIER

SL. NO	MATERIALS	SPECIFICATION	MANUFACTURERS/ SUPPLIER
1	Cyclobenzaprine HCl	USP	Fleming laboratories, Hyderabad.
2	Sugar spheres	IH	Werner, USA.
3	Sucrose blend	USP-NF	Shiva sakthi, Hyderabad.
5	Aerosil (colloidal silicon dioxide)	USP-NF	Evonik, Germany.
6	PVP – k30 (kollidon k30 powder)	USP-NF	BASF, Germany
7	HPMC E5 (Hydroxy propyl methyl cellulose)	USP-NF	Shine-E-tsu, Japan
8	Ethyl cellulose N-50	USP-NF	Feicheing, Chaina.
9	PEG (poly ethylene glycol)6000	USP-NF	Clarient.
10	Talc	USP-NF	Signet chemical corporaton, US.
11	IPA (Iso propyl alcohol)	USP-NF	Ra chem, Hyderabad.
12	Purified water	USP	Ra chem., Hyderabad.

6.2. INSTRUMENTS USED:

Table No: 10 DETAILS OF EQUIPMENTS USED

SR. NO.	*INSTRUMENT*	MANUFACTURER/SUPPLIER.
1.	Electronic Balance	Sartorius, Germany.(ETD - 1020)
2.	Sifter	Bright pharma machinary.
3.	Pulverizer	Micro pulverizer.
4	Blender	Sreenix.(SCLDC 1310)
5	Coating pan	Platinum pharma tech(pptc-18)
6	Tray dryer	Millenium equipment pvt.ltd.(6G)
7	Fluid bed coater	Platinum pharma tech (RPT FBC 5)
8	Friability Test Apparatus	Roche TAR10 Friabilator.
9.	Vernier caliper	Inox- somet.
10.	Disintegration apparatus	Electro Lab.
11	Dissolution apparatus	Electro Lab. TDT - 14L
12	Double beam UV Spectrophotometer	Shimadzu (UV – 2450).
13	FTIR Spectrophotometer	Perkin Elmer spectrum.
14	Digital pH meter	Eutech instruments.
15	Automatic capsule filling machine	Rimek formulations.
16	Melting point apparatus.	Kemi,Mumbai.
17	Tapped density apparatus.	Electrolab (ETD – 1020).
18	Mechanical stirrer	Vision labs.
19	Hand held Sieve	VWR Scientific
20	Stability Chamber	Thermo Lab

6.3. METHODS

6.3.1. INNOVATOR DETAILS[68]

Bonelax capsules are available in two strengths -15 mg, 30mg**.**

Description:

Dosage form and strength:

API Characterization:

Drug: Cyclobenzaprine Hydrochloride

- Description of powder was determined.
- Moisture content was determined.
- Assay was determined by UV method.
- Characteristics like bulk density, tapped density, compressibility index, hausner's ratio and angle of repose were performed.

With the help of analysis of the innovator product we will able to compare the results obtained of our formulated product and it was helpful for calculation of the (f_1) dissimilarity & (f_2) similarity dissolution factor.

6.3.2. Preparation of calibration curve of Cyclobenzaprine HCl in 0.1N HCl:

Cyclobenzaprine Hydrochloride exhibits peak absorbance at 290 nm in 0.1 N HCl. Instrument used: Systronic Double beam UV Spectrophotometer.

Procedure:

Preparation of 0.1N HCl:

Pipette out 8.6 ml of concentrated hydrochloric acid and diluted to 1000ml with distilled water and stirred well.

Procedure for calibration curve:

Weigh accurately 100mg of Cyclobenzaprine Hydrochloride and dissolve it in 100 ml calibrated volumetric flask and completing volume with methanol (Primary stock solution). From the primary stock solution pipette out 10ml into 100 ml calibrated volumetric flask and make up volume with 0.1N HCl. This is the secondary stock solution.

Several dilutions were made from this secondary solution, to obtain a concentration range of 5-25 µg/ml. The absorbance was measured at 290nm using 0.1N HCl as blank and plotted to get the calibration curve.

6.4. PREFORMULATION STUDIES[69]

A preformulation activity ranges from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance.

Preformulation studies are carried out with the objective of ascertaining the incompatibility of the excipients used in the existing formulation and to avoid any excipient, which is incompatible with the drug in the final formulation

Objective:

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substances to formulate into a

dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility index, melting point, molecular weight, sieve analysis.

a) Physical Appearance

The appearance of the API was done by visual observation.

b) Solubility studies [72]

Drugs solubility is usually determined by the equilibrium solubility method by which an excess of drug is placed in a solvent and shaken at a constant temperature over long period until equilibrium is obtained. Chemical analysis of drug content in solution is performed to determine the degree of solubility using rotating shaker.

c) Determination of Melting Point[70]

Melting point of Cyclobenzaprine Hydrochloride was determined by capillary method by using Mel-Temp melting point apparatus.

e) Physical properties:

Density[69]

Density of pellets can be affected by changes in formulation and or process variable.

i) **Bulk density:**

The bulk density of a powder is the weight of the powder divided by the volume it occupies, normally expressed as g/ml. Bulk density is important criteria as it can significantly affect fill volumes, can affect batch size determination during coating operation. The total volume includes particle volume, inter-particle void volume and internal pore volume. The bulk density of powders depends greatly on degree of compaction.

ii) **Tapped density:**

It is defined as the maximum packing density of a powder (or blend of powder) achieved under the influence of well defined, externally applied forces. The minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface

forces including moisture. Therefore, the tap density of a material can be used to predict both its flow properties and its compressibility.

Method:

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal

The bulk density, and tapped density were calculated using the following formulas:

Bulk density (ρ_o) = W / V_o

Tapped density (ρ_t) = W / V_F

Where,

W = weight of the powder

V_O = initial volume

V_F = final volume

iii) Compressibility index (Carr's index)[71]

The bulk density and tapped density was measured and compressibility index was calculated using the formula.

%compressibility index = $[(\rho t-\rho o)/\rho t]\times 100$

Where,

ρt= tapped density, ρo=bulk density.

Table No. 11: Relation between % compressibility and flowability

Compressibility index	Type of flow
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

iv) Hausner's ratio [72]

Hausner's ratio was determined as the ratio between the tapped density to that of the bulk density.

$$\text{Hausner's ratio} = \rho t/\rho o$$

Where,

ρt = tapped density

ρo =bulk density

Table No. 12 : Relation between Hausner's Ratio and flowability

Hausner's ratio	Type of flow
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

v) Flow property [73]

Flow property reflects suitability of material during filling operation. Also it reflects changes in particle size, shape, density, electrostatic charges and adsorbed moisture, which may arise from processing or formulation changes.

The more commonly used method to assess flow properties is angle of repose.

Angle of Repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane and is related to the density, surface area and shapes of the particles. Material with a low angle of repose forms flatter piles than material with a high angle of repose (Tan θ).

$$\tan\theta = h/r$$

Where,

h = height of the pile; r = radius of the base of the pile

Method:

A glass tunnel is held in place with a clamp on ring report over a glass plate, powder (weighed) and poured in tunnel keeping the orifice of tunnel blocked. When powder is emptied from funnel, angle of heap to horizontal plane is measured with protector. Highet of pile (h) and radius of the base (r) is measured with ruler. Thus the angle of repose is measured.

Table No. 13: Relationship between angle of repose & powder flow

Angle of repose	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

6.5. DRUG-EXCIPIENT COMPATIBILITY STUDIES

Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance (Cyclobenzaprine Hydrochloride) and excipients and therefore to select suitability of chemically compatible excipients. The shelf life of product or any other unwanted effects on the formulation determined by using suitable analytical techniques like FTIR, DSC.

Procedure:

1. Homogenous mixtures of drug and excipients were prepared. These mixtures were filled in a 5ml glass vials and self-seal LDPE bags and packed properly.
2. These vials are exposed to 1) 25°C/60% RH 2) 40˚C / 75%RH. Observations for physical appearance are made at 0 week, 2nd week, and 4th week. The samples were withdrawn for analysis of following parameters by UV and KF Method.
    1) Appearance
    2) Moisture content
    3) Assay
    4) Related substances.

Table No. 14: Protocol For drug-excipients compatibility study

S.No	Composition Details	Initial physical description
1	API	White crystalline powder
2	API + Sugar spheres(#24-#30)	Off-white powder contain spherical pellets
3	API+ Sucrose Powder	Off-white powder
4	API + Aerosil	Off-white powder
5	API + Pvpk-30 (1%)	Off-White powder
6	API + ethyl cellulose N-50	Off-White powder
7	API + HPMC E5	Off-white powder
8	API+ Poly ethylene glycol 6000	white powder contain crystalline material
9	API + Talc	Off white crystalline powder
10	API + Isopropyl alcohol	Off-white thick mass
11	API + Purified Water	Off-white thick mass.
12	API + Sugar spheres + Ethyl cellulose N-50+ HPMC E5+Polyethyleneglycol6000+Pvpk30+Talc+Aerosil +I.P.A + Sucrose +Purified Water.	Off-white powder containing lumps

All the samples mentioned above and initial samples were observed for physical characteristics.

FTIR Spectroscopy:

Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (FTIR). The pellets were prepared at high compaction pressure of about 12 psi for 3 minutes by using KBr and the ratio of sample to KBr is 1:100.The pellets thus prepare were mounted in a suitable holder in SHIMADZU IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 625 cm^{-1} in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

Based on the above discussion and reference product, the following excipients were selected for product development.

Table No. 15: Excipients for present formulation

S.No	Excipient	Functional category
1	Sugar spheres	Core material
2	Aerosil	Disintegrant
3	Pvpk-30	Binder
4	Ethyl cellulose N-50	SR polymer
5	HPMC	Solubulizer
6	Poly ethylene glycol 6000	Plasticizer
7	Talc	Glidant
8	Sucrose powder	Diluent
9	Isopropyl alcohol	Vehicle
10	Purified water	Vehicle

6.6. FORMULATION DEVELOPMENT[74]

Based on preformulation data various excipients were selected and their compilation was shown in the below table.

Table No. 16: Trail batches formulas and their quantities as per mg/capcule

S. No	Ingredients	mg/capsule								
	Drug loading	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Cyclobenzaprine hydrochloride	30	30	30	30	30	30	30	30	30
2	Sugar Spheres (#24 - ≠30)	54.4	54.4	54.4	54.4	54.4	54.4	54.4	54.4	54.4
3	Sugar powder	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2
4	Aerosil	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
	Binder solution									
5	Sugar (10%)	1.02	1.02	1.02	1.02	1.02	1.02	__	__	__
6	Pvp k-30 (1%)	2.72	2.72	2.72	2.72	6.8	6.8	6.8	6.8	6.8
7	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	__	__	__
8	I.P.A	__	__	__	__	__	__	Q.S	Q.S	Q.S
	SR coating									
9	Ethyl cellulose N-50	18.36 (13.5%)	16.32 (12 %)	14.96 (11 %)	13.6 (10)	10.88 (8%)	11.56 (8.5 %)	12.24 (9%)	12.92 (9.5 %)	14.28 (10.5 %)
10	HPMC E5	2.04	2.04	2.04	2.04	1.38	1.38	1.38	1.38	1.38
11	P.E.G-6000	1.83	1.63	1.63	1.63	1.29	1.29	1.29	1.29	1.29
12	Talc	__	__	__	__	0.29	0.29	0.29	0.29	0.29
13	I.P.A	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
14	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Pellets were evaluated by physical and chemical parameters. Characteristics like bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose, sieve analysis and assay carried out.

Manufacturing process of Cyclobenzaprine HCl sustained release pellets:

The manufacturing process involved in two stages

1. Drug loading
2. SR coating

Drug loading:

a) Blending

b) Pulverization

c) Binder solution preparation

d) Pelletization

e) Drying

f) Sifting

SR coating:

a) Preparation of coating solution,

b) Coating,

c) Sifting.

6.6.1. DRUG LOADING:

a) Blending:

Transfer Cyclobenzaprine hydrochloride, sugar blend and aerosol into blender one by one and blend the material for 15 minutes. Finally collect in in-process container (IPC) lined with virgin double polyethylene bag.

b) Pulverization:

Pulverize the blended Cyclobenzaprine HCl with excipients through pulverizer fitted with 0.5mm screen and collect the material in-process container (IPC) lined with virgin double polyethylene bag.

c) Binder Solution Preparation:

Take isopropyl alcohol in S.S vessel and slowly add PVP K-30 (kollidon k-30) under continue stirring until to get clear solution.

Filter the above solution through #200 mesh or nylon cloth.

d) Pelletization:

- Use No. #24 and No.#40 mesh. Check the mesh integrity before and after Sieving.
- Sift the sugar spheres through #24 and #24 down pellets through #30 and collect retains and downs separately. Load the sugar spheres (#24 - #30) into coating pan and start the coating pan and allow the beads to rotate.
- Adjust the compressed air pressure to 1.0-2.0 kg/cm^2
- Start the peristaltic pump and adjust to 10 – 40 RPM.
- Start spraying the binder solution adjusting the gun distance (30-40cm).
- Continue spraying until beads become wet
- Stop spraying and add drug mixture in small quantities to the wet beads in the coating pan until the beads are free flowing.
- Adjust the peristaltic pump to 20 – 80 RPM repeat the spraying of binder solution and powder addition till the completion of the drug mixture.
- Note the parameters at every 30 minutes.

e) Drying:

- Check the cleanliness of trays of tray dryer and record.
- Load the wet drug loaded pellets into tray drier trays and load the trays into tray drier.
- Set the inlet temperature around 60^0c to get the bed temperature between 45^0-50^0c
- Unload the pellets after moisture content comes below 2.0% into the in-process container.

f) Sifting:

- Check the cleanliness of vibro sifter. Use No. #18 and #24 mesh. Check mesh integrity before and after sifting. Operate the vibro sifter.
- Sift the dried pellets through #18 and collect #18 retains and passings separately.
- Now pass #18 passings pellets through #24 and collect retains and passings separately.
- Collect the sifted pellets (#18-#24) and RRS separately into the in-process container.

6.6.2. S.R COATING:

a) Preparation of Coating Solution:

i) Dissolve the ethyl cellulose N-50 in isopropyl alcohol with continuous stirring.

ii) Then disperse the HPMC 6cps in the above IPA solution with continuous stirring.

iii) Dissolve separately the PEG-6000 in purified water with continuous stirring and disperse talc in this solution.

iv) Now add the solution of step – 3 into step - 2 with continuous stirring.

v) Finally pass the above solution through #200 mesh or nylon cloth and collect the solution separately.

b) Coating:

- Operate the fluid bed coater and load the drug loaded pellets into FBC bowl.
- Set the inlet temperature to 45^0-55^0C, bed temperature 40^0-45^0C.
- Coat the drug loaded pellets by bottom spray (Wurster) at peristaltic pump rpm of 15-80 and atomizing air pressure of 3.0-5.0kg/cm^2 with coating solution till the coating solution was completed.
- Dry the pellets in FBC for about 15 minutes before unloading.

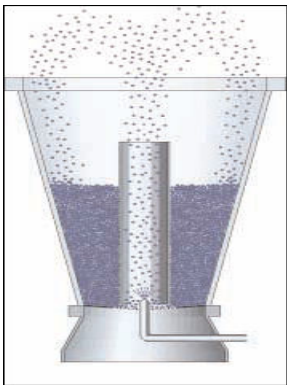


Fig 17: Bottom spray coating

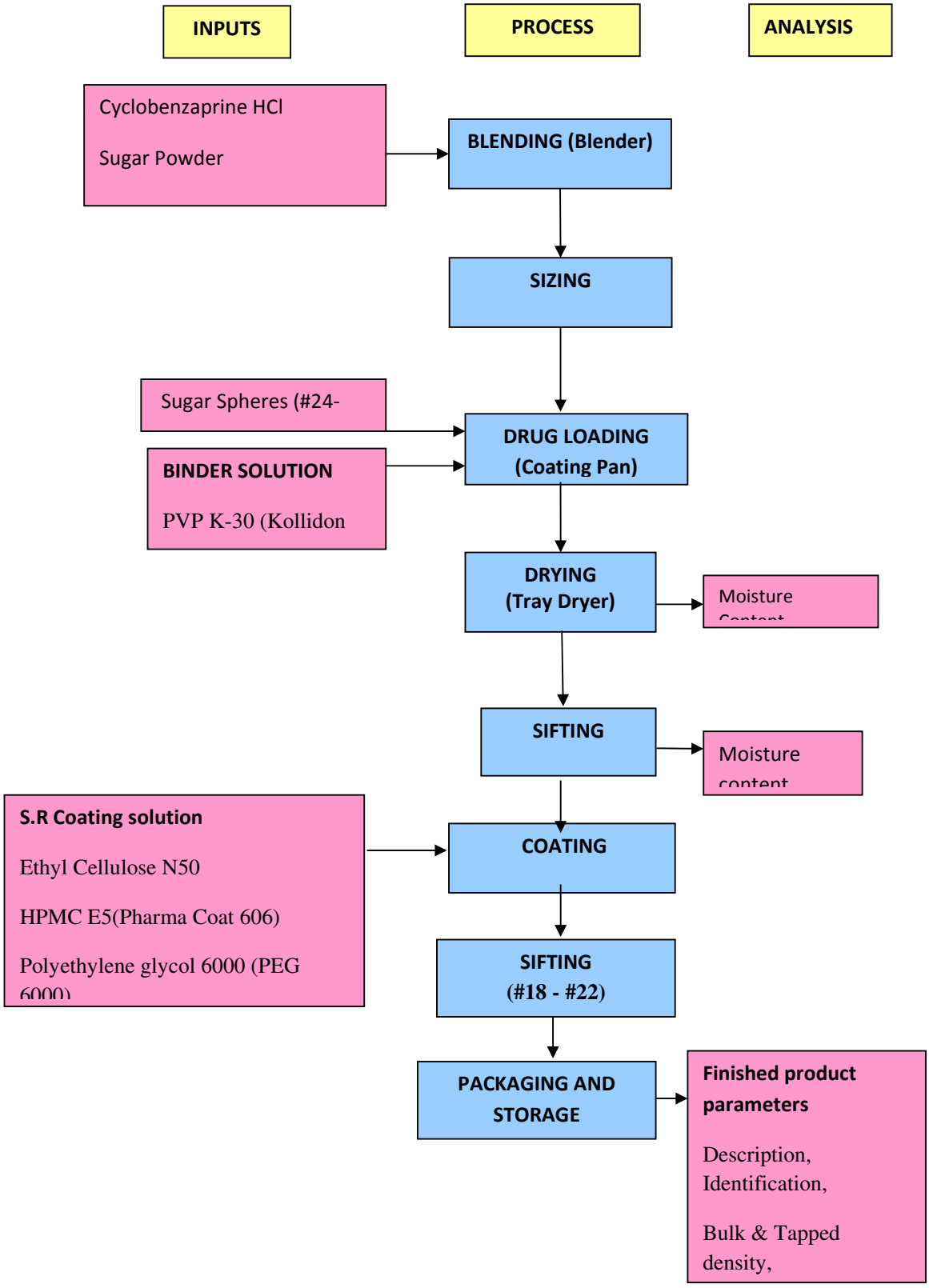
c) Sifting:

- Check the cleanliness of vibro sifter. Use No. #18 and #22 mesh. Check mesh integrity before and after sifting. Operate the vibro sifter.
- Sift the dried pellets through #18 and collect #18 retains and passings separately.
- Now pass #18 passings pellets through #22 and collect retains and gassings separately.
- The sifted pellets (#18- #22) are collected into the in-process container (IPC).

Packaging & Storage:

Collect sifted Cyclobenzaprine HCl pellets (#18-#22) in HDPE container lined with double polyethylene bags. Transfer the HDPE containers into finished goods store and store below 25^0C.

Cyclobenzaprine Hydrochloride sustained release capsules were prepared. The process was displayed in the below flow chart.


INPUTS
PROCESS
ANALYSIS
Cyclobenzaprine HCl
Sugar Powder
BLENDING (Blender)
SIZING
Sugar Spheres (#24-
BINDER SOLUTION
PVP K-30 (Kollidon
DRUG LOADING (Coating Pan)
DRYING (Tray Dryer)
Moisture
SIFTING
Moisture content
S.R Coating solution
Ethyl Cellulose N50
HPMC E5(Pharma Coat 606)
Polyethylene glycol 6000 (PEG 6000)
COATING
SIFTING (#18 - #22)
PACKAGING AND STORAGE
Finished product parameters
Description, Identification,
Bulk & Tapped density,

There are various in process control parameters should be performed. They are

A) During drug layering:

Appearance

Average weight

Weight uniformity

Disintegration time

B) During SR coating:

Appearance

Size of pellets by passing through Sieve

Assay

Coating process parameters

Table No. 17:

Parameters	**Laboratory Scale**
Equipment Partitions: Number/Diameter Number of Spray Guns	7" Wurster 1/89 mm/1
Batch size	1 kg
Coating process parameters	
Fluidizing air volume (CFM)	320 -650
Inlet air temperature (ºC)	50-55
Product bed temperature (ºC)	40-45
Spray rate (g/min)	15-30
Atomizing air pressure (bar)	3.0 – 5.0
Coating Efficiency	99%

6.7. FILLIING OF CYCLOBENZAPRINE HYDROCHLORIDE PELLETS IN CAPSULES

To prepare Cyclobenzaprine Hydrochloride capsules 30 mg by taking Cyclobenzaprine Hydrochloride pellets from the formulation F8 and filled.

Procedure

1. Before filling pellets into capsules the parameters like bulk density, tapped density, compressibility index, angle of repose, Hausner's ratio is evaluated.

2. Size'4' capsules were selected for capsule formulation which has dark blue color body and dark blue color cap.

3. The coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 30mg of Cyclobenzaprine Hydrochloride by Automatic capsule filling machine.

6.8. EVALUATION TESTS:

All the prepared capsules were evaluated for following parameters.

6.8.1. Weight variation test:

The uniformity of dosage units may be demonstrated by determining weight variation and/or content uniformity. The weight variation method is as follows.

Individual weights of 10 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 5 %.

6.8.2 Friability test:

It is necessary to attain acceptable friability of pellets that can withstand handling, shipping, storage and operations like coating and filling. Friability is strongly affected by type and amount of binder used. It is affected by method of processing.

Friability is generally determined by use of Roche TAR 10 frabilator (Erweka, Ensenstam, Germany). It involves placing measured weight of pellets(accurately 5grams) in the friabilator and rotating /tumbled for a predetermined number of revolutions(200) at 25 rpm along with 12 steel balls(diameter 8.5mm, weighing 2.487 gm each) as attrition agents. After friability testing the pellets were sieved (mesh#30).The weight loss(%F) after friability testing was calculated by the formula

$$\%F = (w_i - w_r) X100/w_r$$

Where w_i is the initial weight of the pellets before friability testing, and w_r was the weight of the pellets retained above the sieve (aperture size0.355mm) after friability testing. All parameters were evaluated for 6 times (n=6)

6.8.3 Locked length

It was tested by using vernier calipers.

6.8.4 Disintegration

The compendial disintegration test for hard and soft capsules follows the same procedure and uses the same apparatus described later in this chapter for uncoated tablets. The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºc and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

6.8.5 Moisture Content (By kf method method):

Take about 30 ml of the dried methanol in the KF titration flask and titrate with KF reagent until the end point to make inside of the flask water free. Finely powder pellets of Cyclobenzaprine hydrochloride. Transfer quickly an accurately weighed quantity of about 0.5gm of sample to the titration flask and dissolve by stirring and titrate with KF reagent to the end point and calculate % water content by following formula.

Calculation:

% Moisture content= V x F x 100 / V x 1000

Where,

V= Volume of KF consumed for sample reading,

F= Factor for KF reagent,

W= Weight of sample in g.

6.8.6 Assay (By UV):

Standard preparation:

Transfer about 25 mg of Cyclobenzaprine hydrochloride, accurately weighed, to a 100ml volumetric flask add 70ml of ethanol, sonication for 10 minutes and dilute with methanol to volume. Mix and filter. Transfer 2.o ml of this solution to 50 ml volumetric flask, dilute with methanol to the volume and mix.

Sample preparation:

Powder the pellets and transfer an accurately weighed quantity of the powder equivalent to about 25 mg of Cyclobenzaprine hydrochloride to a 100ml volumetric flask, add 70 ml of methanol, sonicate for 30 minutes and cool the solution to room temperature dilute with methanol to volume. Mix and filter. Transfer 2.0 ml of this solution to a 50 ml volumetric flask, dilute with methanol to volume and mix.

Procedure:

Measure the absorbance of standard and sample preparations in 1 cm cell on suitable UV spectrophotometer at 290 nm, using methanol as blank. Record the absorbance.

Calculation:

% content of Cyclobenzaprine hydrochloride

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{2}{50} \times \frac{100}{WT} \times \frac{50}{2} \times \frac{P}{100} \times 100 = \text{---------}\%$$

% content of Cyclobenzaprine = % content of Cyclobenzaprine Hydrochloride
Hydrochloride ----------X100
% Label claim

Where,

AT = Absorbance of Cyclobenzaprine hydrochloride in sample solution.

AS = Absorbance of Cyclobenzaprine hydrochloride in standard solution.

WS = Weight of Cyclobenzaprine hydrochloride working standard taken in mg.

WT = weight of the sample taken in mg.

P = purity of Cyclobenzaprine hydrochloride working standard used.

6.8.7 *IN-vitro* Dissolution studies :

Dissolution (By UV):

Dissolution parameters:

Medium : 0.1n HCl,

Volume : 900ml

Apparatus : USP Apparatus II (paddle)

RPM : 50

Temperature : 37 ± 0.5 °C

Time intervals : 2^{nd} hour, 4^{th} hour, 8^{th} hour, 12^{th} hour, 16^{th} hours.

Standard preparation:

Transfer about 50 mg of Cyclobenzaprine hydrochloride accurately weighed, to a 100ml volumetric flask add 70ml of methanol, sonication for 10 minutes and dilute with methanol to volume. Mix and filter. Transfer 2 ml of this solution to a 100ml volumetric flask, dilute with medium to the volume and mix.

Sample preparation:

Set the parameters of dissolution apparatus as mentioned above transfer the capsules equivalent to 30 mg of Cyclobenzaprine hydrochloride each individual bowls and operate the dissolution apparatus, withdraw 10ml of the sample solution after 2nd hour, 4th hour, 8th hour, 12th hour, 16th hour from each dissolution jar and replace with same volume of dissolution medium previously maintained at 37.0 ± 0.5^0c.

Procedure:

Measure the absorbance of standard and sample preparation in 1 cm cell on suitable UV spectrophotometer at 290 nm, using medium as blank. Record the absorbance.

Calculation:

% Labelled amount of Cyclobenzaprine hydrochloride dissolved (D_n)

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{2}{50} \times \frac{100}{WT} \times \frac{50}{2} \times \frac{P}{100} \times 100 = \text{---------}\%$$

Where,

AT = Absorbance of Cyclobenzaprine hydrochloride in sample solution.

AS = Absorbance of Cyclobenzaprine hydrochloride in standard solution.

WS = Weight of Cyclobenzaprine hydrochloride working standard taken in mg.

WT = weight of the sample taken in mg

P = purity of Cyclobenzaprine hydrochloride working standard used

Calculation for correction factor:

For 2nd Hour = D2

For 4th Hour = D4+CF2

For 8th Hour = D8+CF2

For 12th Hour = D12+CF8+CF4+CF2

For 16th Hour = D16+CF12+CF8+CF4+CF2

Procedure:

Dissolution of the capsules of each batch was carried out using USP dissolution type II apparatus using paddle at 50 rpm. The dissolution was studied using 900 ml of 0.1N HCl for 16 hours . The temperature was maintained at 37 ± 0.2 °C. With draw 10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through What man filter paper and discard first few ml of the filtrate. Dissolution study was carried out in pH 0.1 N HCl for 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 16^{th} hours and samples were suitably diluted and analyzed for Cyclobenzaprine hydrochloride content at 290 nm by UV method.

Data Treatment of Dissolution Studies:

1. Dissolution profiles of % DR Vs time were obtained. Amount of drug released at 16^{th} hour in 0.1N HCl followed by 2^{nd}, 4^{th}, 8^{th}, 12^{th}, 16^{th} hours were calculated.
2. Mechanism of drug release was obtained by applying the release data to various models like zero order, first order, Higuchi and Korsmeyer equation / Peppa's model

6.8.8 SCANNING ELECTRON MICROSCOPY (SEM) OF THE OPTIMIZED FORMULATION:

SEM has been used to determine particle size distribution, surface topology, texture and to examine the morphology of fractured or sectioned surface. The SEM generally used for generating three dimensional surface relief images derived from secondary electrons.

The surface of drug pellets and coated pellets were examined under a scanning electron microscopy. The pellets were mounted onto stubs using double sided adhesive tape. The mounted samples were sputter coated under an argon atmosphere with gold palladium and examined at 15 KV accelerating voltage.

6.9. Dissolution Profile Comparison Using Similarity factor f2 and Difference factor f1

The comparison of final optimized formulation compared with the innovator product by using similarity and dissimilarity factor, the F1and F2 was respectively

6.9.1. Calculation of similarity (f2) and dissimilarity (f1) factors:

a) Similarity factor (f2):

The similarity factor F2 was defined as a logarithmic reciprocal square root transformation of ne plus the mean square difference in percent dissolved between the tests and reference products.

This was calculated to compare the test with reference release profiles. It was calculated from the mean resolution data according to the following equation.

$$F2=50\times \log\{[1+(1/n)\sum nt=1 (Rt-Tt)2]\times 100\}$$

Where,

n = number of full point

Rt = the reference profile at the time points t

Tt = the test profile at the same point

The method is more adequate to compare the dissolution profiles when more than three or four dissolution time points are available and can be applied if average difference between Rt and Tt is >100.

b) Difference factor or dissimilarity factor (f1):

Difference factor describes the relative error between two dissolution profiles. It is approximately the percentage error between curves. The percent error is zero when the test and reference profiles are identical and increases the proportionality with the dissimilarity between the two profiles. Dissimilarity factor or difference factor (F1) was calculated from the following equation.

$$F1= \{[\sum nut=1 (Rt-Tt)]/ \sum nit=1 Rt]\} \times 100$$

Table no. 18: Similarity factor range

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

6.10 *IN-VITRO* RELEASE KINETIC MODELS

The results of in vitro release profile obtained for all the formulations were plotted in models of data treatment as follows: -

1. Zero - order kinetic model - Cumulative % drug released versus time.
2. First – order kinetic model - Log cumulative percent drug remaining versus time.
3. Higuchi's model - Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model - Log cumulative percent drug released versus log time.

6.10.1. Zero Order Model:[4]

This model describes the systems where the release rate is independent of the concentration of the dissolved species (Shan Yang L., 1998). The dissolution data are fitting into the zero order equation

$$A_t = A_0 – K_0t,$$

Where,

A_t= Amount of drug released at time't',

A_0= Initial drug concentration,

K_0= Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order kinetics and its slope is equal to Zero order release constant K_0.

This relation can be used to describe the drug dissolution of several types of sustained release pharmaceutical dosage forms, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc.

6.10.2. First Order Model: [4]

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species

Release behavior generally follows the following first order equation:

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where

C = the amount of drug dissolved at time 't',

Co = the amount of drug dissolved at t=0 and,

K = the first order rate constant (hr^{-1}).

A graph of log amount of drug release vs. time yields a straight line. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

6.10.3 Higuchi Model:[75]

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation

$$f_t = K_H \cdot t^{1/2}$$

Where

f_t = fraction of drug released at time 't',

K_H = Higuchi rate constant.

The Higuchi square root equation describes the release from systems where the solid is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

6.10.4. Korsmeyer equation / Peppa's model[76]

To study the mechanism of drug release from the sustained-release matrix tablets, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_\alpha = Kt^n$$

Where,

M_t / M_α = the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get: -

$$\text{Log } M_t / M_\alpha = \text{Log } K + n \text{ Log } t$$

Table No.19: MECHANISM OF DRUG RELEASE AS PER KORSMEYER EQUATION / PEPPA'S MODEL.

S. No.	n Value	Drug release
1.	< 0.45	Fickian release
2.	0.45 < n <1.0	Non – Fickian release
3.	> 1.0	Class II transport

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n'. For Fickian release 'n' = 0.45 while for anomalous (non-Fickian) transport 'n' ranges between 0.45 and 1.0.

6.11. ACCELERATED STABILITY STUDY[77, 78]

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

Storage conditions

Stability samples are stored at

Accelerated : 40±2°C/75±5% RH

Intermediate: 30±2°C/65±5% RH

Long term : 25±2°C/60±5% RH

Testing Intervals for

Accelerated: Initial, 1, 2, 3 & 6 months

Long term: Initial, 3, 6, 9, 12, 18, 24 & 36 months.

Intermediate: Initial, 3, 6, 9 & 12 months.

The formula of F8 was optimized and selected for evaluation studies. Further stability study was done for F8.

Evaluation of samples:

The samples were analyzed for the following parameters,

- **Physical evaluation:**

  Appearance: The samples were checked for any change in colour at every week.

- **Chemical evaluation**:

  Drug content: The samples were checked for drug content.

  Drug release: The samples were subjected to drug release studies.

In general significant change for a drug product is defined as

- A 5% change in assay from its initial value or failure to meet the acceptance criteria for when using biological or immunological procedures.
- Any degradation products exceeding its acceptance criterion.
- Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. E.g. size, shape and dose delivery per activation however some changes in physical attributes may be accepted under accelerated condition and as appropriate for the dosage form.
- Failure to meet the acceptance criterion for pH.
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.

Studies like moisture content, assay, dissolution studies were carried out for a period of 2 months. Initial stage, at the end of first month and second month, the above said parameters were carried out at 25^{O}C/60%RH, 30^{O}C/65% RH and 40^{O}C/75%RH.

7. RESULTS & DISCUSSION

7.1. INNOVATOR DETAILS:

7.1.1. Description:

Bonelax capsules are available in two strengths -15 mg, 30mg**.**

7.1.2. Dosage form and strength:

- Bonelax capsules are blue color body, red color cap with "Bonelax 30mg" imprinted on the capsule.
- They are available in 30/100 capsules per container.

API Characterization:

- **Drug:** Cyclobenzaprine Hydrochloride

Identification (By UV):

- The UV absorption spectrum obtained with the sample in the assay preparation corresponds to that of the standard preparation as obtained in the assay.

7.1.3. Evaluation:

Moisture content:

- Moisture content was determined by KF method and it was found to be 1.71%.
- For pellets Characteristics like bulk density, tapped density, compressibility index, hausner's ratio and angle of repose were performed.

Table no. 20: Physical properties

Bulk density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index	Hausner's Ratio	Angle of repose
0.830	0.883	6.002	1.063	26 °.62''

- **Assay:**

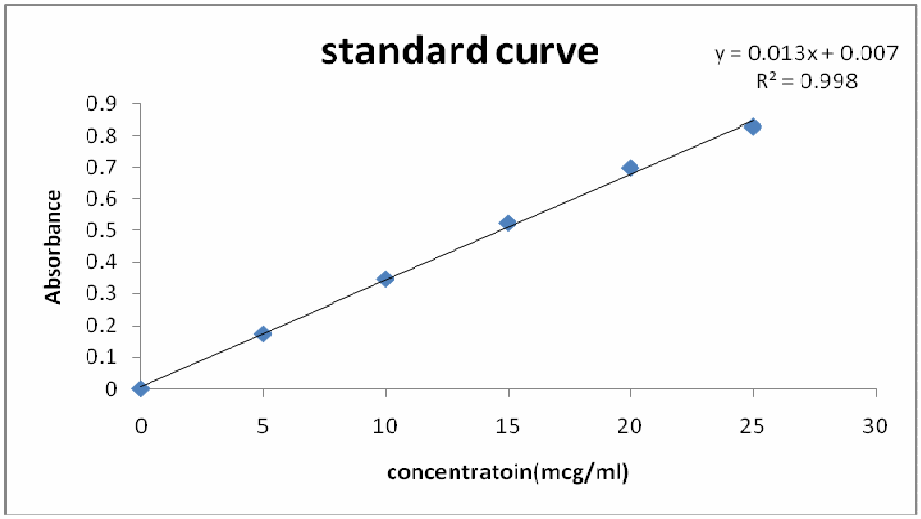
Assay was determined by UV method and it was found to be 99.8%.

7.2. Preparation of Calibration curve of Cyclobenzaprine Hydrochloride

Calibration curve of Cyclobenzaprine Hydrochloride was determined by plotting concentration v/s absorbance at 290 nm. The results were show in table.

Table No. 21: STANDARD CURVE OF CYCLOBENZAPRINE HYDROCHLORIDE IN 0.1N HCl

Concentration in µg/ml	Absorbance at 290nm
0	0
5	0.174
10	0.345
15	0.523
20	0.698
25	0.827



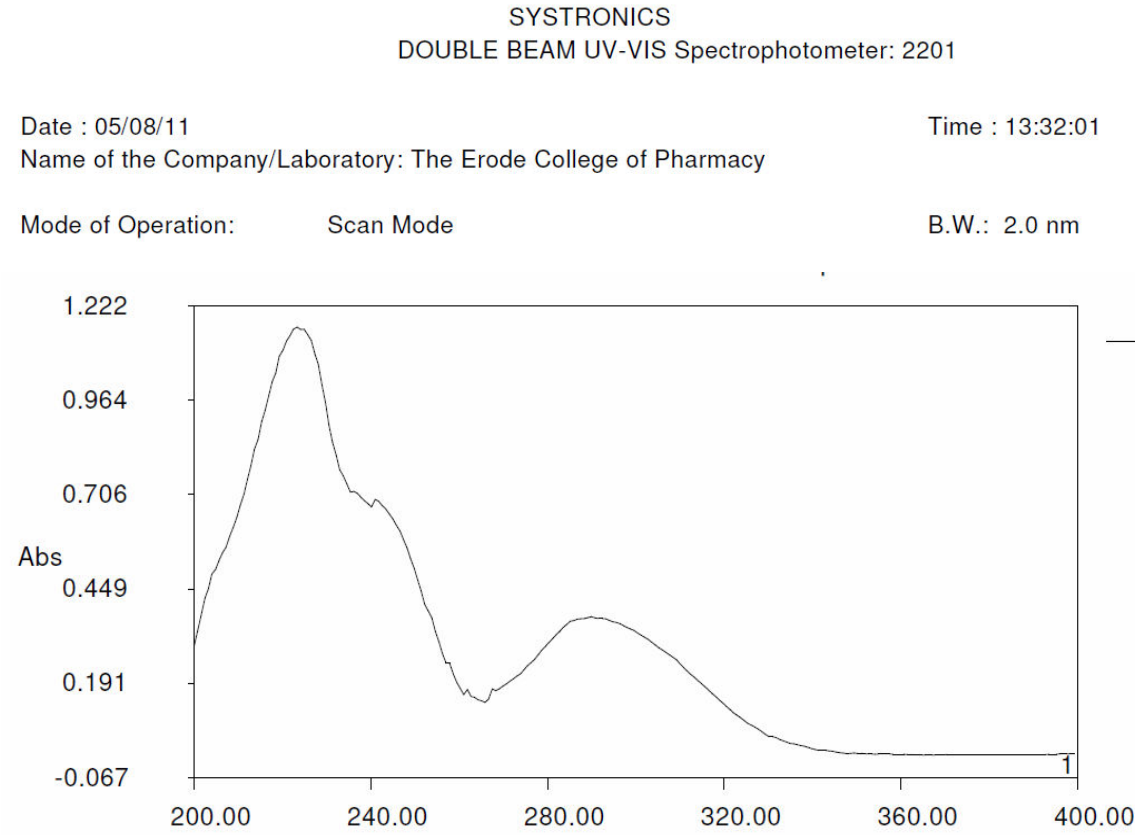
Graph No. 1: Standard curve of Cyclobenzaprine hydrochloride in 0.1 N HCl.

The Slope = 0.013

The correlation coefficient = 0.998

From the standard curve of Cyclobenzaprine Hydrochloride, it was observed that the drug obeys Beer's law in concentration range 5-25 µg/ml in 0.1N HCl

7.3. Determination of λ_{max} of Cyclobenzaprine Hydrochloride :



Graph No. 2: UV Spectrum of Cyclobenzaprine Hydrochloride

The λ_{max} of Cyclobenzaprine Hydrochloride was determined by UV spectrum the graph indicates that the maximum absorbance was observed at 289.6nm. The λ_{max} value was near to that reported in analytical profile[57].

7.4. PREFORMULATION STUDIES

a) Physical Appearance

Cyclobenzaprine Hydrochloride was observed visually and it appeared as a white crystalline salt

b) Solubility

Solubility studies were conducted and the results are

Table no. 22: Solubility of drug

solvent	solubility
water	Freely soluble
Ethanol	Freely soluble
Isopropanol	Sparingly soluble
chloroform	Slightly soluble
Methylene chloride	Slightly soluble
Hydrocarbons	Insoluble
chloroform	Insoluble

c) **Melting Point Determination**

The Melting point of Cyclobenzaprine Hydrochloride was determined by capillary method and it was found to be 216^0C while reported melting point range 215-219^{o}c, which complies with USP standards, indicating purity of the drug sample.

d) Physical properties

Physical properties of Cyclobenzaprine Hydrochloride like bulk density, tapped density, compressibility index, hausner's ratio and angle of repose result were

Table No. 23: Physical properties of Cyclobenzaprine Hydrochloride API

Bulk density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index	Hausner's Ratio	Angle of repose
0.284	0.426	33.3	1.5	36.5

7.5. Compatibility Study

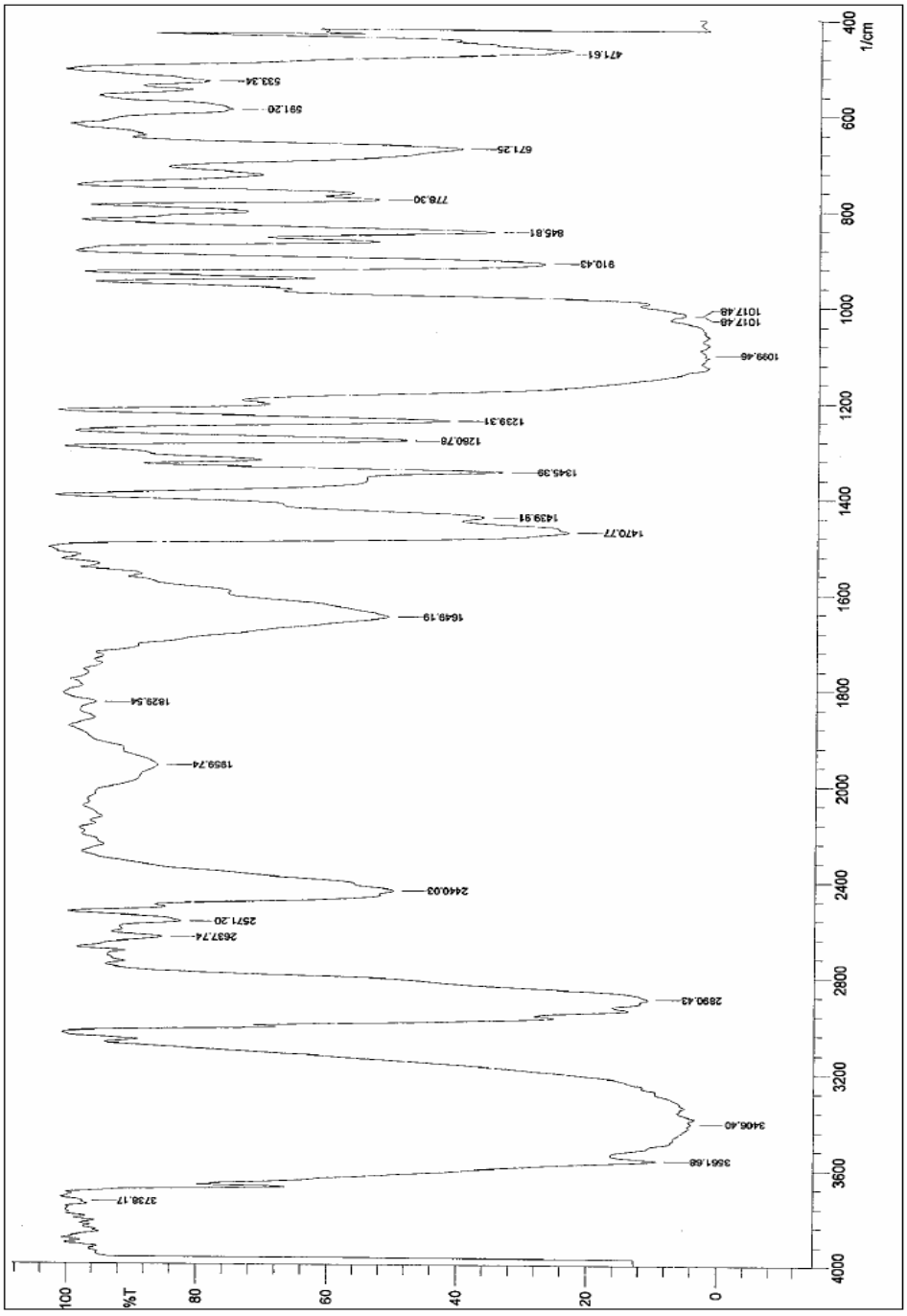
The drug and excipient combinatoins were taken and the samples were observed every week for any color change or lumps formation. For this samples stored at 40^0C/75%RH and the samples were checked at the end of 1,2 and 4^{th} weeks.The results of physical observation were shown in table.

Table No. 24: Compatibility study of drug and excipients

S. No.	Drug and Excipients	Initial Physical Description	40°C / 75% RH (Closed)		
			1st Week	2nd Week	4th Week
1	API	White crystalline powder	*	*	*
2	API + Sugar spheres(#24#30)	Off-white powder contain spherical pellets	*	*	*
3	API+ Sugar Powder	Off-white powder	*	*	*
4	API + Aerosil	Off-white powder	*	*	*
5	API + Pvpk-30 (1%)	Off-White powder	*	*	*
6	API + Ethyl cellulose N-50	Off-White powder	*	*	*
7	API + HPMC E5	Off-white powder	*	*	*
8	API+ Poly ethylene glycol 6000	white powder contain crystalline material	*	*	*
9	API + Talc	Off white crystalline powder	*	*	*
10	API + Isopropyl alcohol	Off-white thick mass	*	*	*
11	API + Purified Water	Off-white thick mass.	*	*	*
12	API + Sugar spheres + Ethyl cellulose N-50 + HPMC E5 +Polyethylene glycol 6000+Pvpk30+Talc+Aerosil +Isopropyl alcohol + Sucrose+ Purified Water.	Off-white powder containing lumps	*	*	*

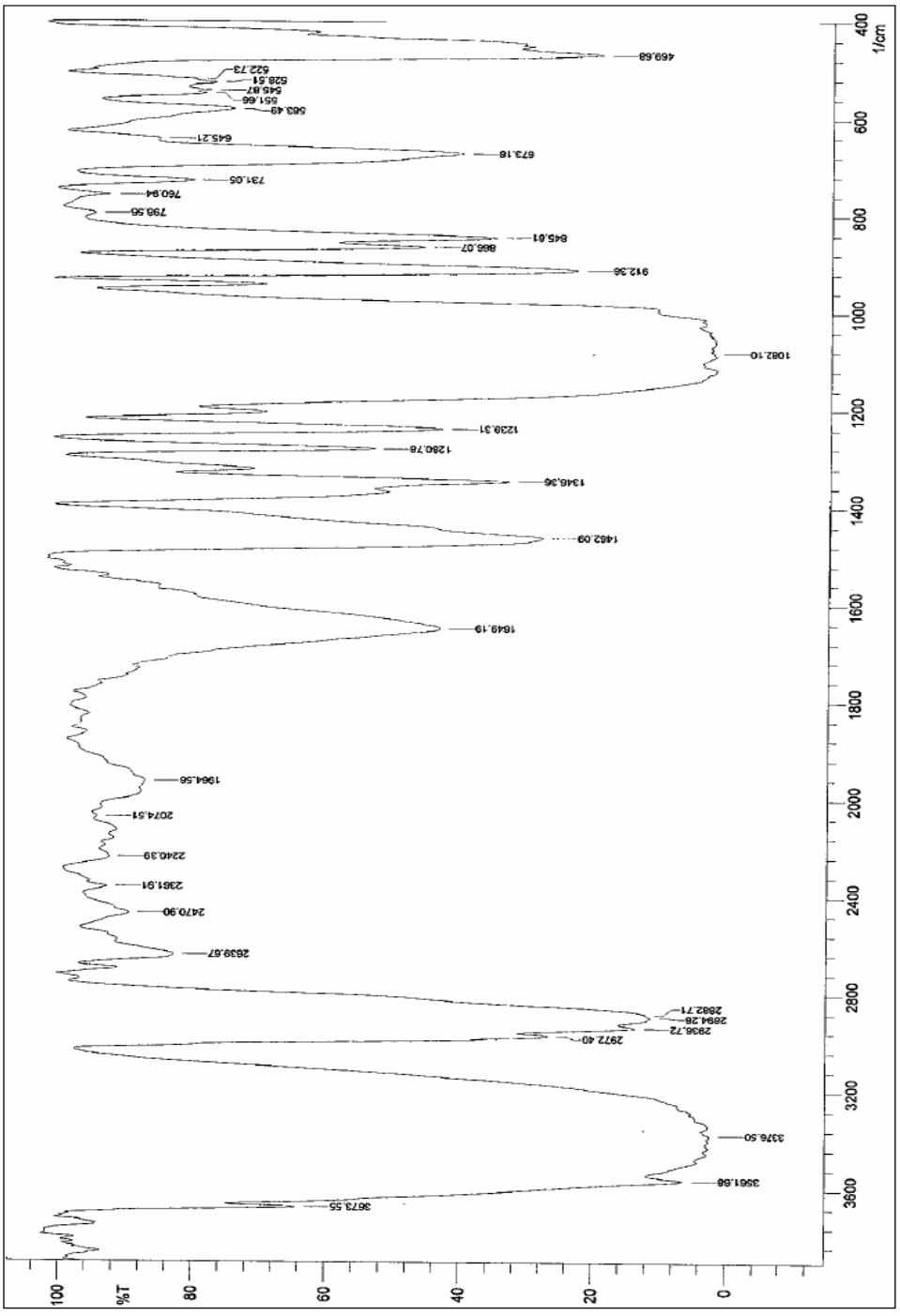
Note: Star mark (*) indicates that there was no interaction between drug and excipients at 40°C/75% RH.

IR SPECTRUM OF PURE CYCLOBENZAPRINE HYDROCHLORIDE



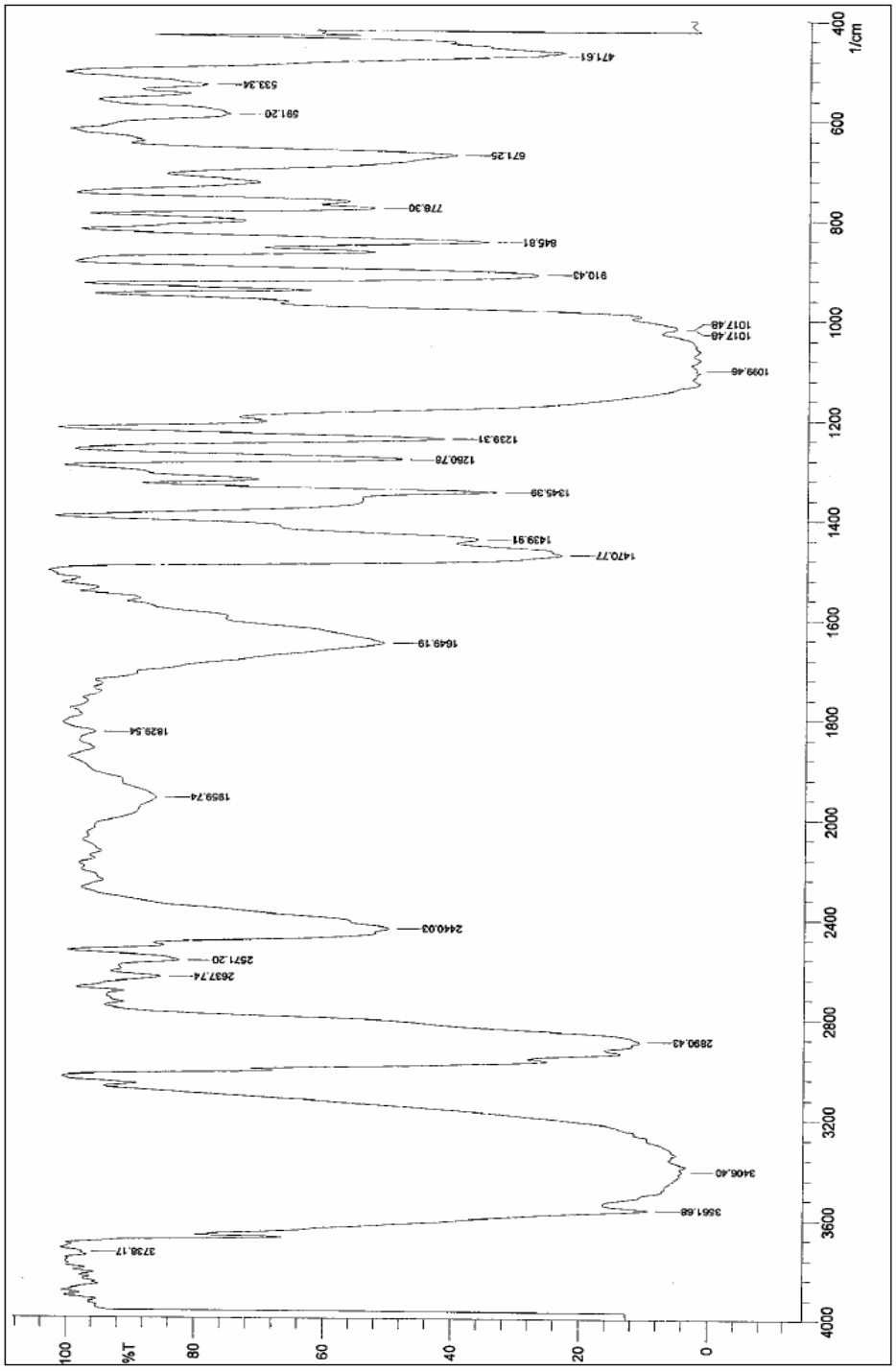
Spectra No.1: Cyclobenzaprine Hydrochloride.

IR SPECTRUM OF EXCIPIENTS



Spectra No.2 : Excipients

IR SPECTRUM OF CYCLOBENZAPRINE HCL + EXCIPIENTS



Spectra no.3: Cylobenzaprine HCl+ Excipients

Table No. 25: INTERPRETATION OF FT-IR SPECTRA OF CYCLOBENZAPRINE HYDROCHLORIDE

S.No	Functional Category	Standard IR range (cm^{-1})	Assessment of peak in Drug (cm^{-1})
1	Skeletal ring stretching vibraton in aromatic ring	1300-1600	1319.35, 1435.09, 1530.57, 1594.22
2	C-H stretching in aromatic ring	3000-3100	3060.17
3	Overtone of C-H bending in aromatic ring	1600-2000	1790.97
4	C-H Symmetric stretching of $-CH_2$ group in tertiary amine	2660-2820	2635.81
5	C-H bending vibraton of $–CH_2$ group in tertiary amine	1445-1485	1481.38
6	C-N stretching	1020-1220	1167.94
7	C-H inplane bending in cycloheptane ring	722 or less	689.57

Table No. 26: COMPATABILITY STUDIES

S.No	Functional Category	Standard IR range (cm^{-1})	Ranges of peak in mixture (cm^{-1})
1	Skeletal ring stretching vibraton in aromatic ring	1300-1600	1345.37, 1439.91, 1470.77, 1510.22
2	C-H stretching in aromatic ring	3000-3100	2890.43
3	Overtone of C-H bending in aromatic ring	1600-2000	1649.19
4	C-H Symmetric stretching of $-CH_2$ group in tertiary amine	2660-2820	2637.74
5	C-H bending vibraton of $-CH_2$ group in tertiary amine	1445-1485	1470.77
6	C-N stretching	1020-1220	1099.46
7	C-H inplane bending in cycloheptane ring	722 or less	671.25

Compatibility studies were performed using FT-IR spectrophotometer to find out any physical as well as chemical alteration of the drug characteristics. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. From the results, it was concluded that there was no interference in the functional group as the principle peaks of the Cyclobenzaprine hydrochloride were found to be unaltered in the drug-polymer physical mixture, indicating that they were compatible chemically.

7.7. EVALUATION TESTS

Weight variation test:

No Significant difference was observed in the weight of individual capsules from the average weight. Capsule weights of all batches were found within recommended USP limits.

Friability test:

Friability of all formulations showed %friability less than 1% that indicates ability of pellets (capsules) to with stand shocks, which may encountered.

Disintegration test:

Capsules of all batches Disintegrate within 5 minutes, which indicates acceptable limits.

Locked length:

The values of all capsules locked length observed were within the limits.

Table No. 28: Evaluation parameters of filled capsules of all Formulations F1-F9

Formulation code	Evaluation Parameter		
	Average Weight Variation(n=10) (mg)	Disintegration Time(n=5) (min)	Locked Length(n=5) (mm)
F1	178.3±0.351	4.70±0.06	12.5±0.9
F2	179.0±0.378	4.50±0.04	12.2±0.9
F3	173.6±0.325	4.40±0.02	11.9±0.7
F4	177.5±0.348	5.10±0.07	11.7±0.5
F5	176.6±0.350	4.60±0.05	11.8±0.8
F6	174.9±0.332	4.90±0.07	11.5±0.6
F7	174.4±0.329	4.80±0.06	12.3±0.9
F8	175.7±0.342	4.25±0.02	11.2±0.2
F9	177.5±0.349	4.58±0.03	11.6±0.7

7.7.5. Moisture content test:

Table No. 29: Moisture content & Friability values of Pellets F1-F9

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Moisture content	3.2%	2.9%	3.2%	3.6%	3.3%	2.9%	2.3%	1.75%	1.8%
2	Friability	0.54%	0.50%	0.42%	0.56%	0.61%	0.51%	0.44%	0.33%	0.35%

7.7.6. Assay:

The sustained release pellets prepared were evaluated for assay and the results for assay of all formulations (F1-F9) were given in the following table

Table No. 30: Assay results

Formulation	Assay values (%) Specification: 99-101%
Reference	99.9
F1	89.8
F2	95.1
F3	98.7
F4	94.5
F5	104.8
F6	97.0
F7	100.7
F8	99.7
F9	98.1

From the above results, the sustained release pellets prepared were compared with the reference specification .The assay of formulation F5, F7 & F8 were found to be within the limits.

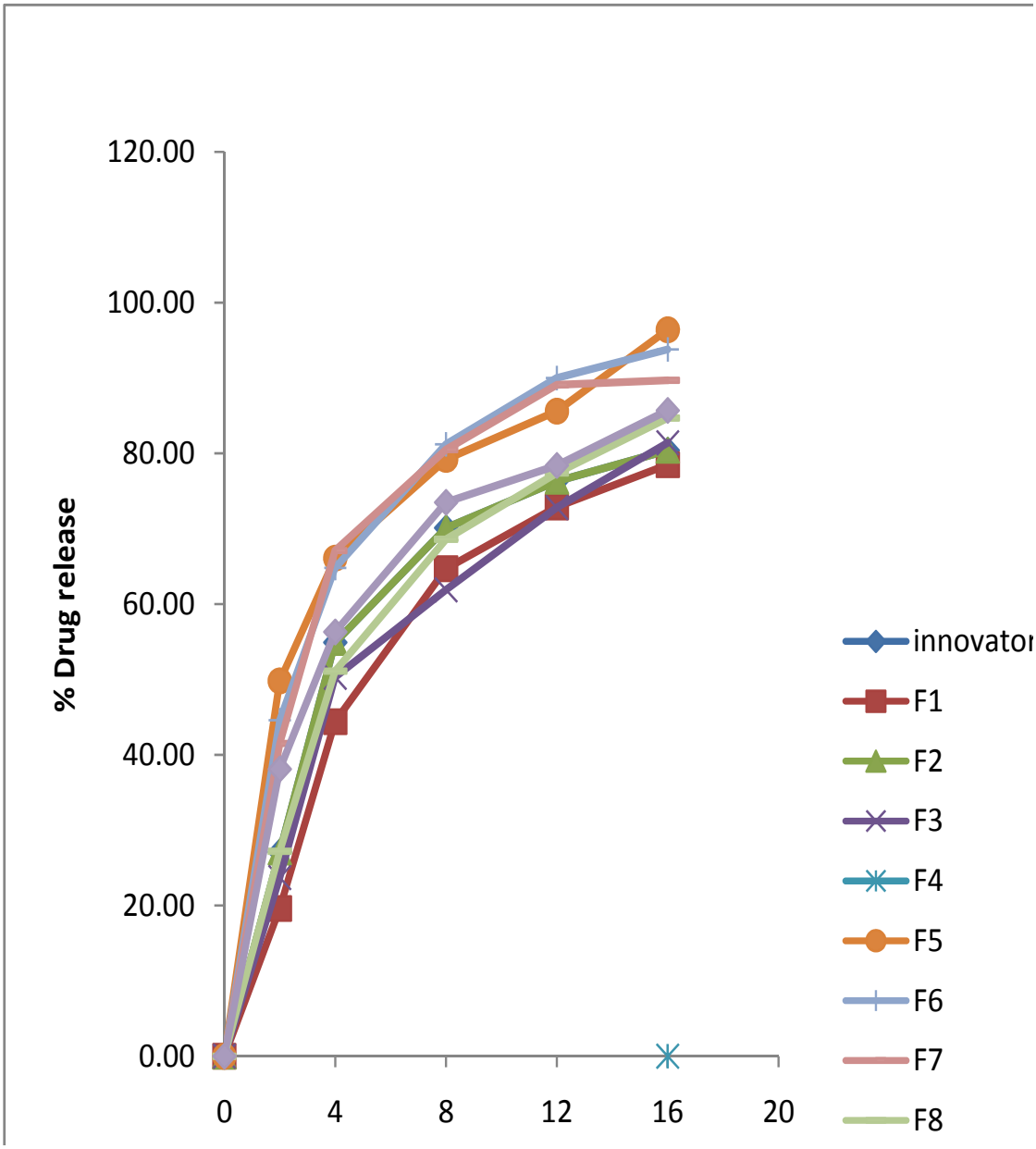
7.7.7. *IN-VITRO* DRUG RELEASE STUDIES:

Table No. 31:In-Vitro Release Profile of INNOVATOR:

Time (hours)	Cumulative % Drug released Acid stage (0.1N HCl)
0	0
2	27.1
4	54.9
8	70.1
12	76.3
16	80.4

Table No. 32: Cumulative % Drug release of Formulation F1 to F9

Time hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	19.6	37.7	23.7	31.4	49.8	44.6	41.5	27.2	38.1
4	44.4	62.1	50.3	54.9	66.1	64.8	67.1	51.1	56.3
8	64.7	70.8	61.9	69.6	79.2	81.2	80.5	68.6	73.5
12	72.9	79.5	72.8	76.4	85.2	90.0	89.1	77.4	78.4
16	78.5	80.6	81.4	87.5	96.4	93.8	89.7	84.7	85.7

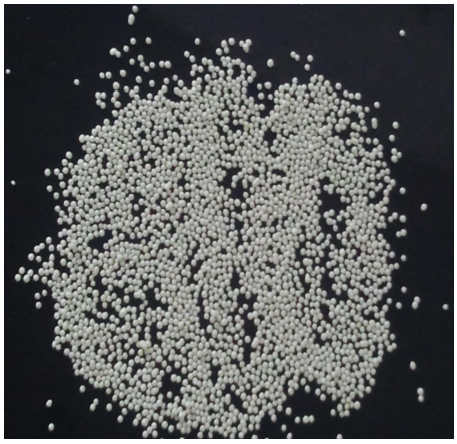


Graph No. 3 : Comparative *in-vitro* release profiles of F1-F9 with Innovator

7.6. OPTIMIZED FORMULATION:

Table No.27: Characteristics of pellets of Formulation F8

CORE PELLETS	RESULTS
For uncoated Pellets	
Yield (Limit NLT 97%)	99.6%
Bulk density	0.726
Tapped density	0.768
Compressibility index	5.46
Hausner's ratio	1.057
Angle of repose	26.43
Sieve analysis (100gm)	
# 18 passed	99g
# 24 retained	99g
#18 passed& #24 retained	99g
For coated Pellets	
Yield (Limit NLT 97%)	98%
Bulk density	0.832
Tapped density	0.885
Compressibility index	5.98
Hausner's ratio	1.06
Angle of repose	26.56
Sieve analysis (100gm)	
# 18 passed	98g
# 22 retained	98g
#18 passed& #22 retained	98g



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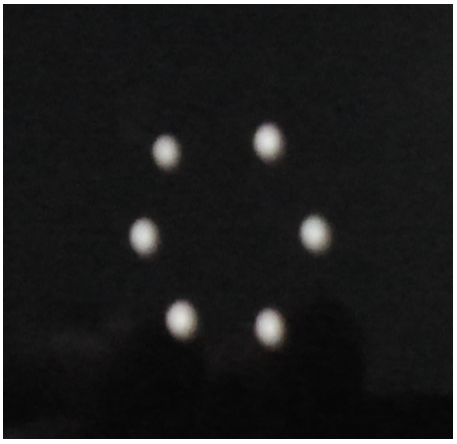

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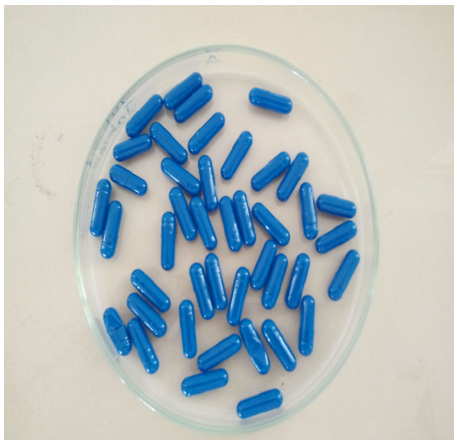

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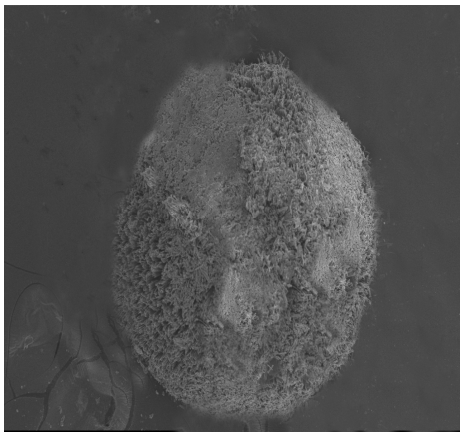


D

Fig. No:19

A – Photograph of prepared pellets

B – Microscopic photograph of pellets

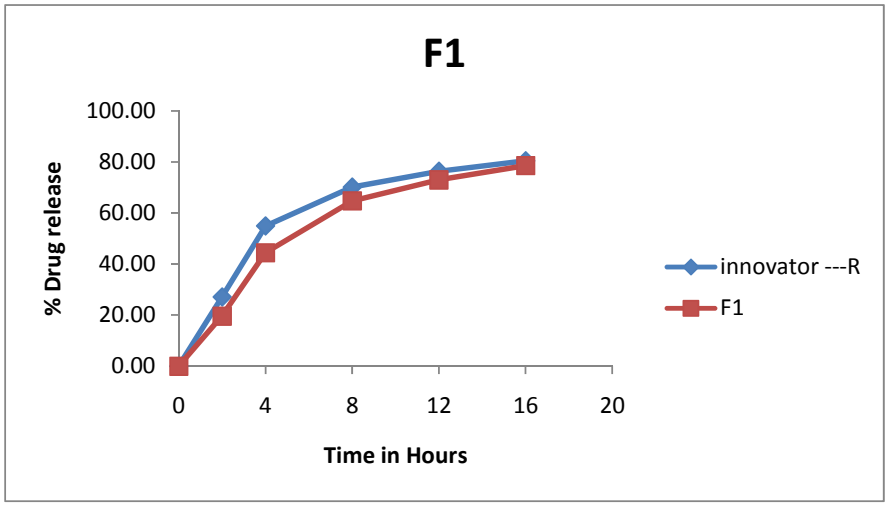
C - Photograph of prepared capsules

D –Shape and Size of pellet (70x) SEM

7.9. COMPARATIVE DISSOLUTION STUDIES:

Table No. 33: Comparative Dissolution Profile of F1 with Innovator:

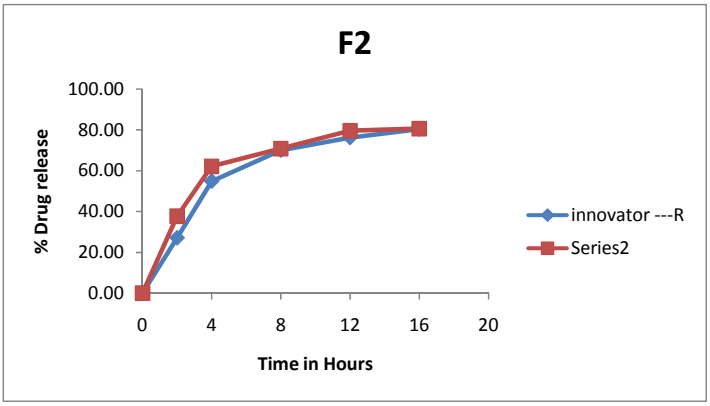
Time in min	INNOVATOR (R)	F1(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	**0**	**0**	**0**	
2	27.10	19.6	7.5	56.25	7.5	**59.12**
4	54.90	44.4	10.5	110.25	10.5	**f1 value**
8	70.10	64.7	5.4	29.16	5.4	
12	76.30	72.9	3.4	11.56	3.4	**9.29**
16	80.40	78.5	1.9	3.61	1.9	
Total	308.8	280.1	28.7	210.83	28.7	



Graph No. 4 : Comparative dissolution profile of F2 with innovator.

Table No. 34: Comparative Dissolution Profile of F2 with Innovator:

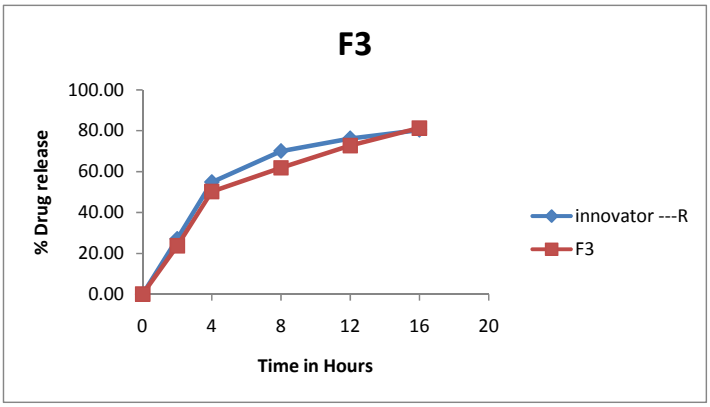
Time in min	INNOVATOR (R)	F2(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	37.7	-10.6	112.36	10.6	**61.09**
4	54.90	62.1	-7.2	51.84	7.2	**f1 value**
8	70.10	70.8	-0.7	0.49	0.7	
12	76.30	79.5	-3.2	10.24	3.2	**7.09**
16	80.40	80.6	-0.2	0.04	0.2	
Total	308.8	330.7	-21.9	174.97	21.9	



Graph. No. 5: Comparative dissolution profile of F2 with innovator.

Table No. 35: Comparative Dissolution Profile of F3 with Innovator:

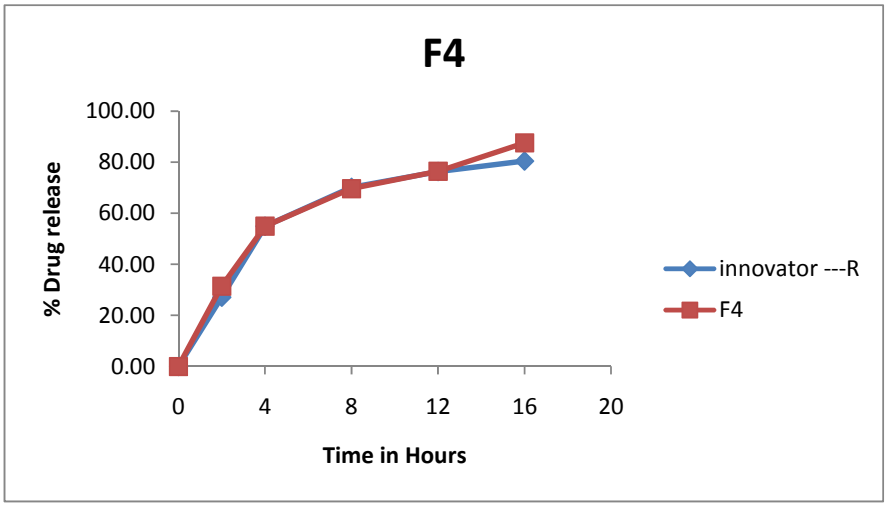
Time in min	INNOVATOR (R)	F3(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	23.7	3.4	11.56	3.4	**65.66**
4	54.90	50.3	4.6	21.16	4.6	**f1 value**
8	70.10	61.9	8.2	67.24	8.2	
12	76.30	72.8	3.5	12.25	3.5	**6.70**
16	80.40	81.4	-1.0	1.0	1.0	
Total	308.8	290.1	18.7	113.21	20.7	



Graph No. 6: Comparative dissolution profile of F3 with innovator.

Table No. 36: Comparative Dissolution Profile of F4 with Innovator:

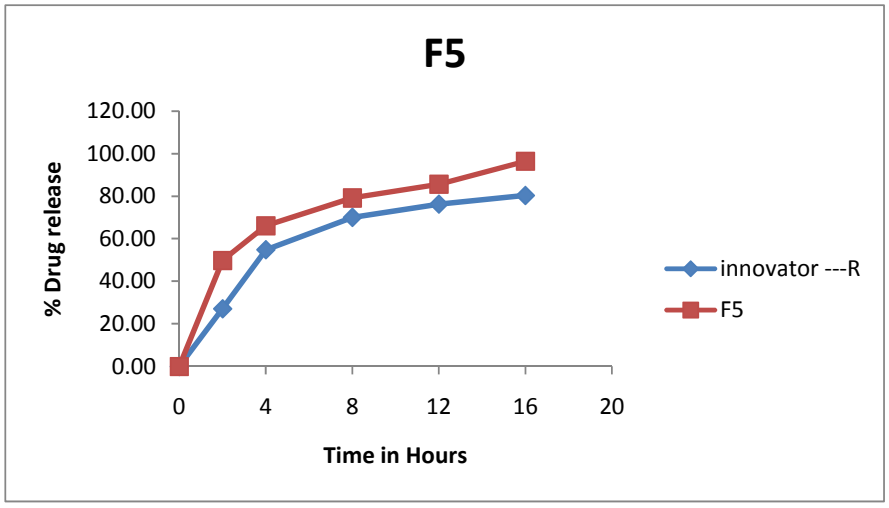
Time in min	INNOVATOR (R)	F4(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	31.4	-4.3	18.49	4.3	**70.72**
4	54.90	54.9	0.0	0.0	0.0	**f1 value**
8	70.10	69.6	0.50	0.25	0.50	
12	76.30	76.4	-0.10	0.01	0.10	**3.89**
16	80.40	87.5	-3.10	50.41	3.10	
Total	308.8	319.8	-11.0	69.16	12.0	



Graph No. 7 : Comparative dissolution profile of F4 with innovator.

Table No. 37: Comparative Dissolution Profile of F5 with Innovator:

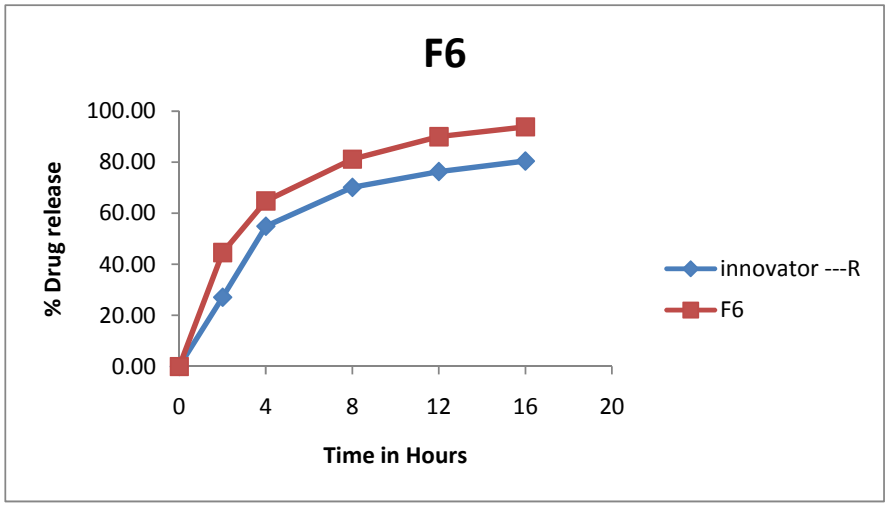
Time in min	INNOVATOR (R)	F5(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	49.8	-22.70	515.24	22.70	**41.73**
4	54.90	66.1	-11.20	125.44	11.20	**f1 value**
8	70.10	79.2	-9.10	82.81	9.10	
12	76.30	85.6	-9.36	86.49	9.36	**22.12**
16	80.40	96.4	-16.00	256.00	16.00	
Total	308.8	377.1	-68.3	1066.03	68.3	



Graph No.8 : Comparative dissolution profile of F5 with innovator.

Table No. 38: Comparative Dissolution Profile of F6 with Innovator:

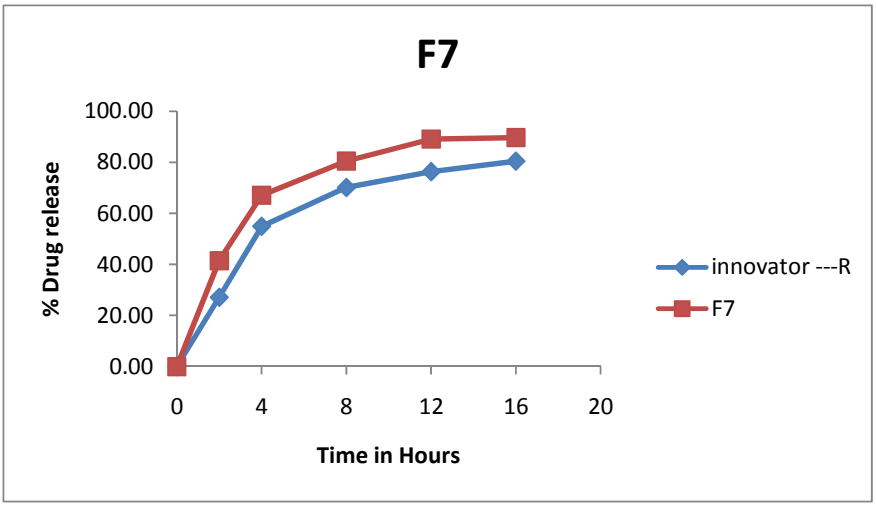
Time in min	INNOVATOR (R)	F6(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	44.6	-17.5	306.25	17.5	**43.62**
4	54.90	64.8	-9.9	98.01	9.9	**f1 value**
8	70.10	81.2	-11.10	123.21	11.10	
12	76.30	90.0	-13.7	187.69	13.7	**21.42**
16	80.40	93.8	-13.4	179.56	13.4	
Total	308.8	374.4	-65.6	894.72	65.6	



Graph No. 9 : Comparative dissolution profile of F6 with innovator.

Table No. 39: Comparative Dissolution Profile of F7 with Innovator:

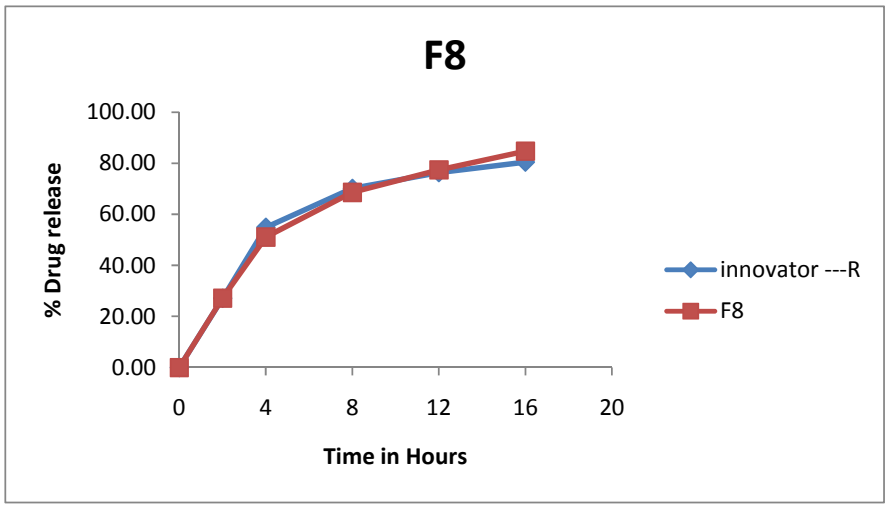
Time in min	INNOVATOR (R)	F7(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	41.5	-14.4	207.36	14.4	**46.05**
4	54.90	67.1	-12.2	148.84	12.2	**f1 value**
8	70.10	80.5	-10.4	108.16	10.4	
12	76.30	89.1	-12.8	163.84	12.8	**19.14**
16	80.40	89.7	-9.3	86.49	9.3	
Total	308.8	367.9	-59.1	714.69	59.1	



Graph No. 10 : Comparative dissolution profile of F7 with innovator.

Table No. 40: Comparative Dissolution Profile of F8 with Innovator:

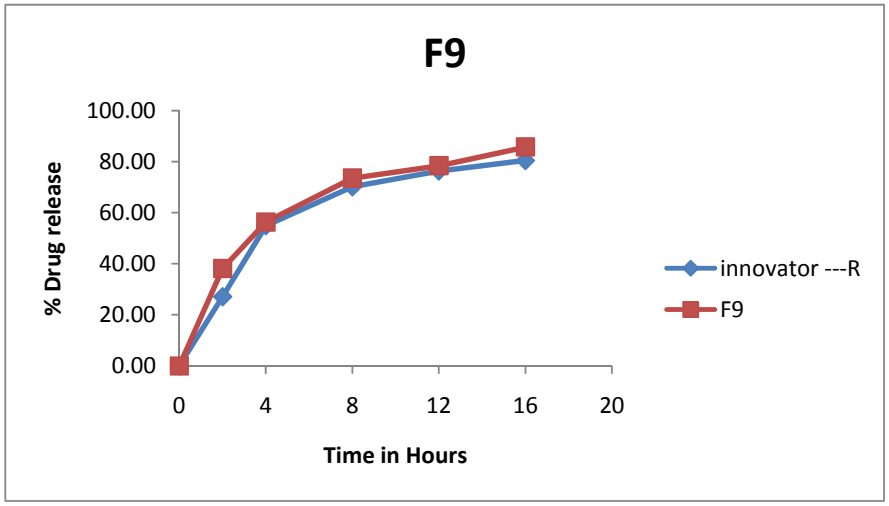
Time in min	INNOVATOR (R)	F8(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	27.2	0.10	0.01	0.10	**77.05**
4	54.90	51.1	3.8	14.44	3.8	**f1 value**
8	70.10	68.6	1.5	2.25	1.5	
12	76.30	77.4	1.10	1.21	1.10	**3.50**
16	80.40	84.7	4.30	18.49	4.30	
Total	308.8	309.0	-0.20	36.40	10.80	



Graph No.11 : Comparative dissolution profile of F8 with innovator.

Table No. 41: Comparative Dissolution Profile of F9 with Innovator:

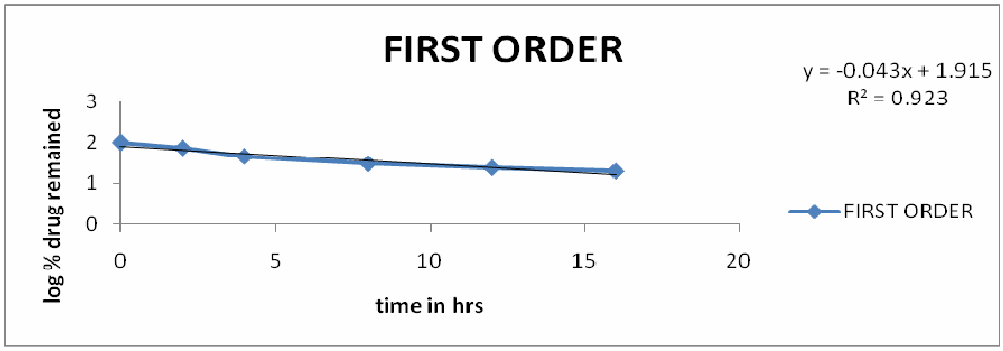
Time in min	INNOVATOR (R)	F9(T)	Rt-Tt	$(Rt-Tt)^2$	[Rt-Tt]	f2 value
0	0	0	0	0	0	
2	27.10	38.1	-11.0	121.00	11.0	**61.58**
4	54.90	56.3	-1.40	1.96	1.40	**f1 value**
8	70.10	73.5	-3.40	11.56	3.40	
12	76.30	78.4	-2.10	4.41	2.10	**7.51**
16	80.40	85.7	-5.30	28.09	5.30	
Total	308.8	332.0	-23.2	167.02	23.2	

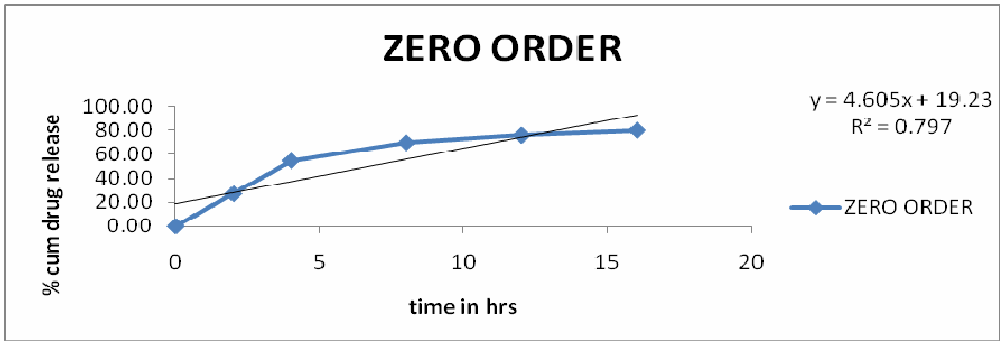


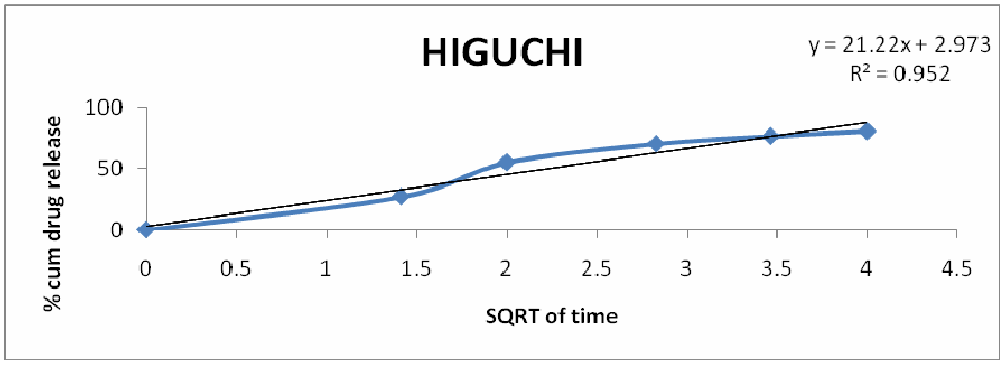
Graph No. 12 : Comparative dissolution profile of F9 with innovator.

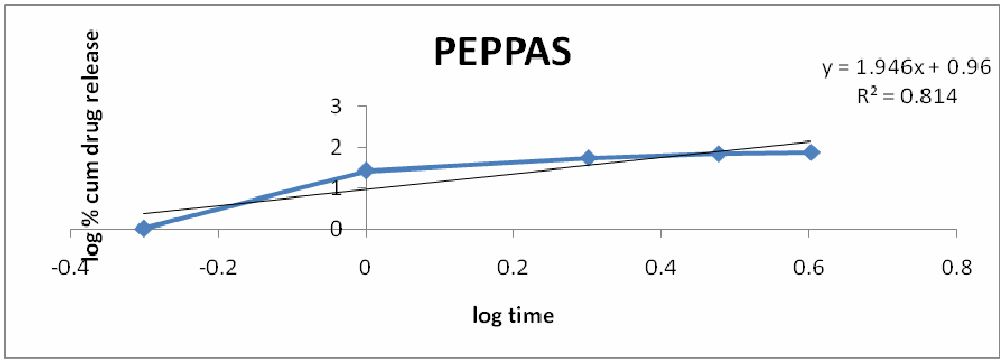
In-vitro drug release profiles of all formulations were carried out by using 0.1N HCl as dissolution medium for about 16 hours. From the results obtained it was observed that F8 with ethyl cellulose N-50 (9.5%) showed 84.7% drug release at the end of 16 hours. Whereas different concentrations of ethyl cellulose 8%, 8.5%, 9% (F5, F6,F7) showed release about 96.4%, 93.8%, 89.7% in 16 hours. It was found to show fast release when compare to innovator and these batches were fail to meet similarity factor. The batches F1, F2, F3, F4 with 13.5%, 12%, 11%, 10% of ethyl cellulose showed release about 78.5%, 80.6%, 81.4% and 87.5% in 16 hours. It was found to show slow release or similar to innovator but failure to meet assay specifications. The batch (F9) with 10.5% ethyl cellulose concentration showed the release of 85.7% in 16 hours, the release of this found was near to innovator but fail to reproducibility of results. Variations in the release concentration of HPMC E5 and PEG 6000 affected the drug release rates. From the above results it was found that the release of drug from ethyl cellulose N-50 9.5% (F8) gave the better drug release and highest similarity factor (77.5) when compare to that other formulations with a optimum concentration. On increase in the polymer concentration drug release declined while decreasing the polymer concentration drug release fast. The formulation F8 was found to give best release with 84.7% (cumulative % drug release) in 16 hours

7.10. *In-vitro* RELEASE KINETIC MODELS

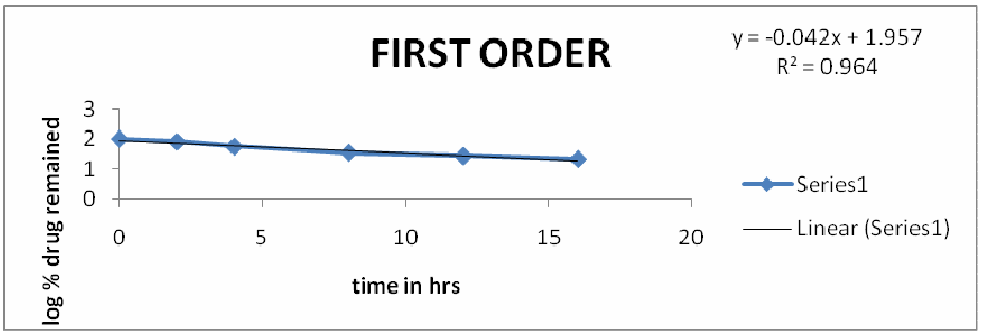


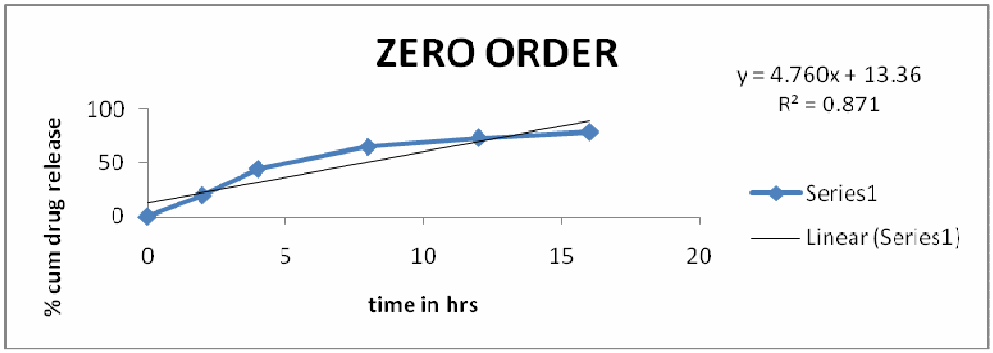


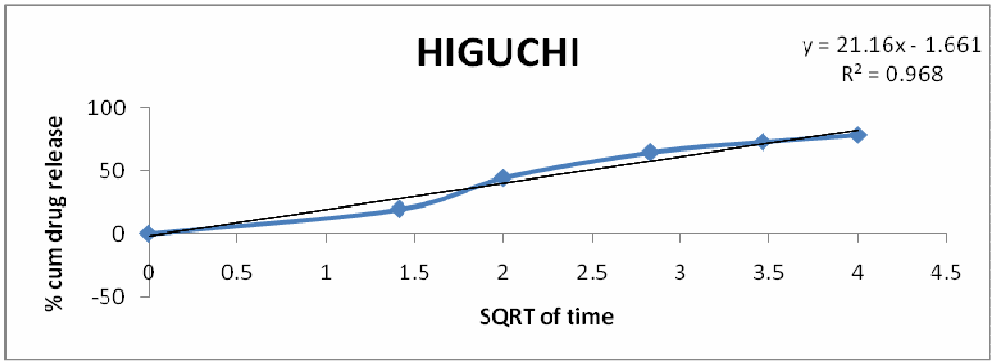


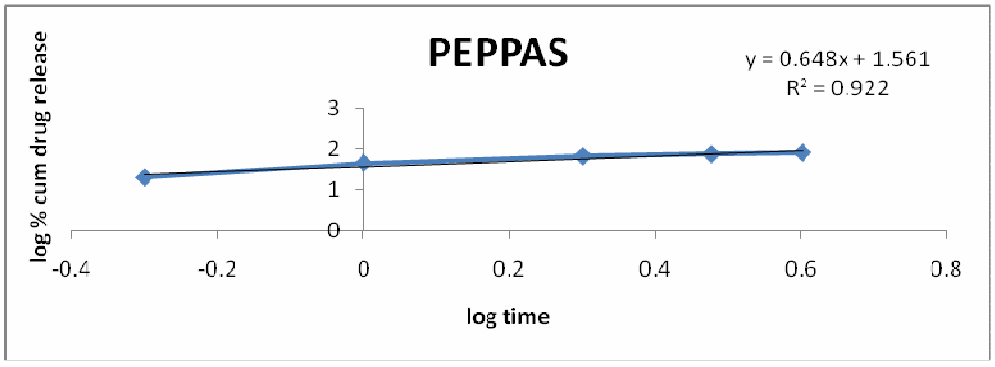


Graph No. 13 : *In-vitro* release kinetic models of Innovator

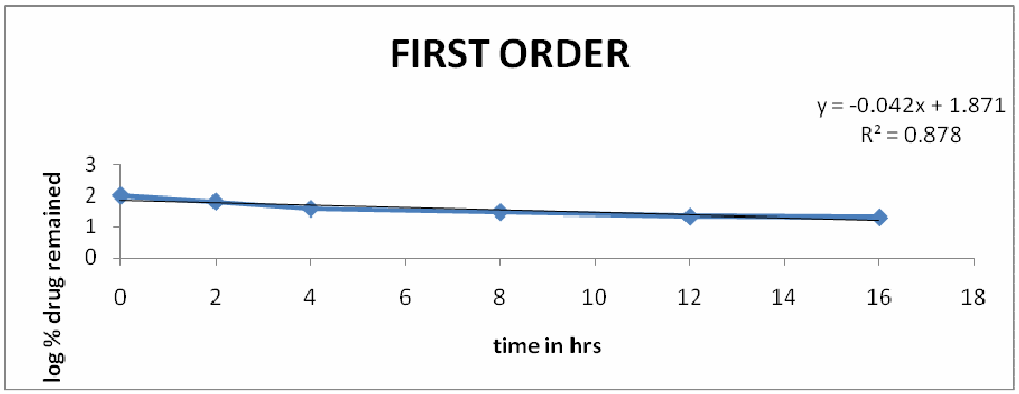


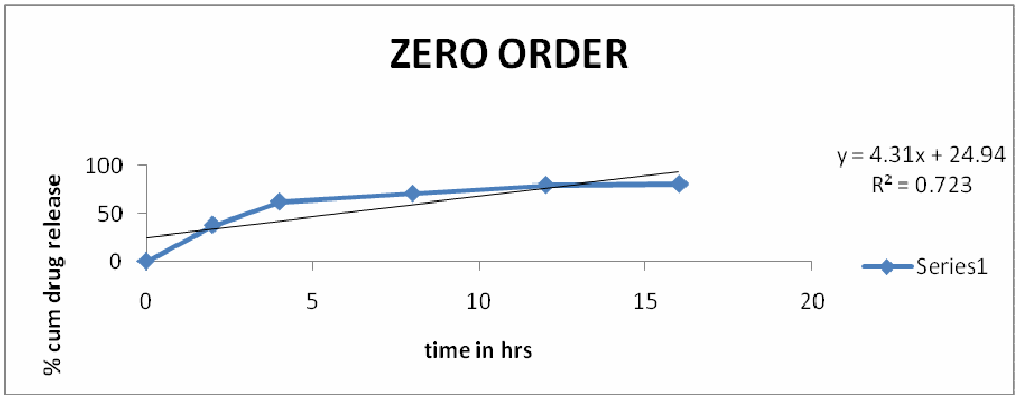


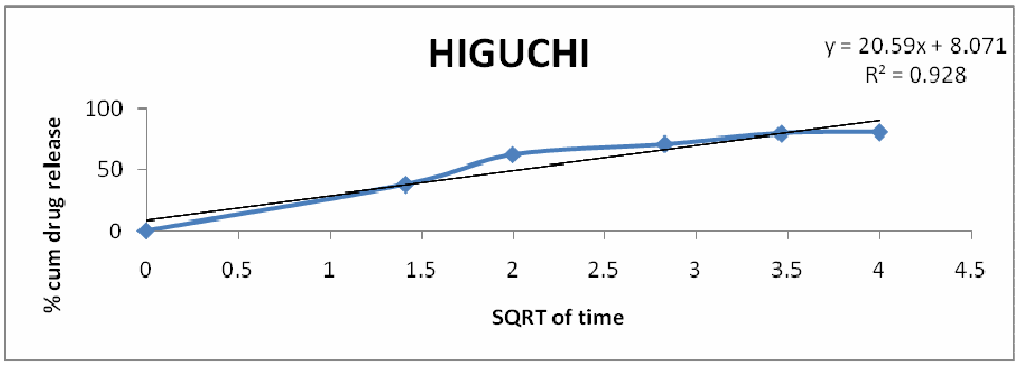


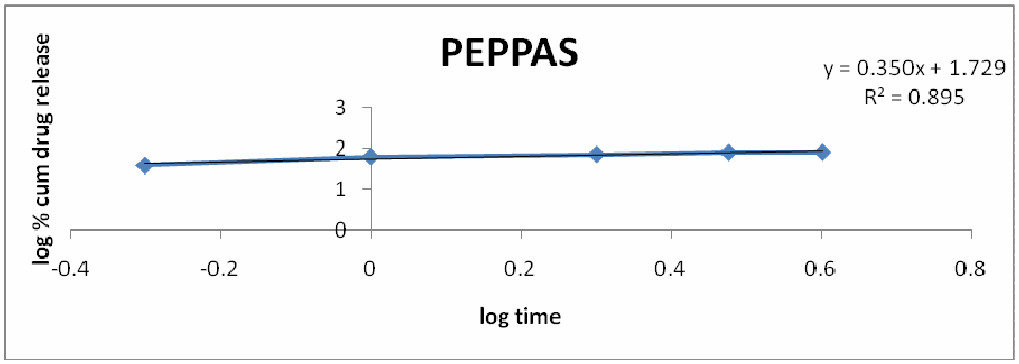


Graph No. 14 : *In-vitro* release kinetic models of **F1**

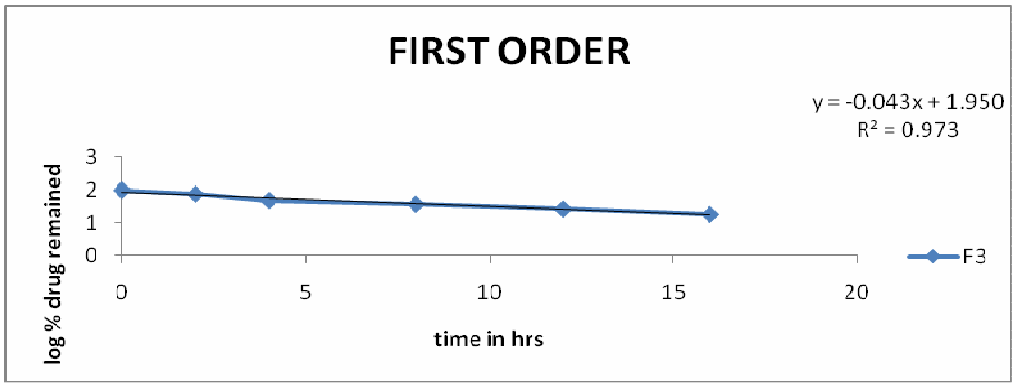


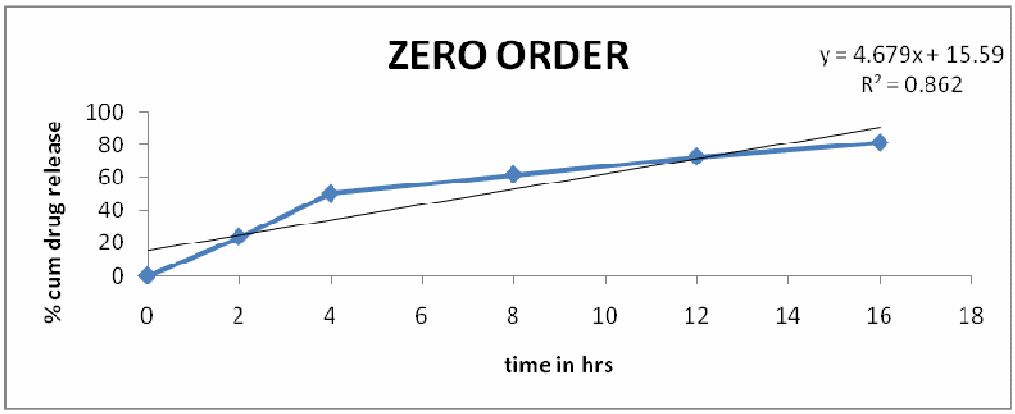


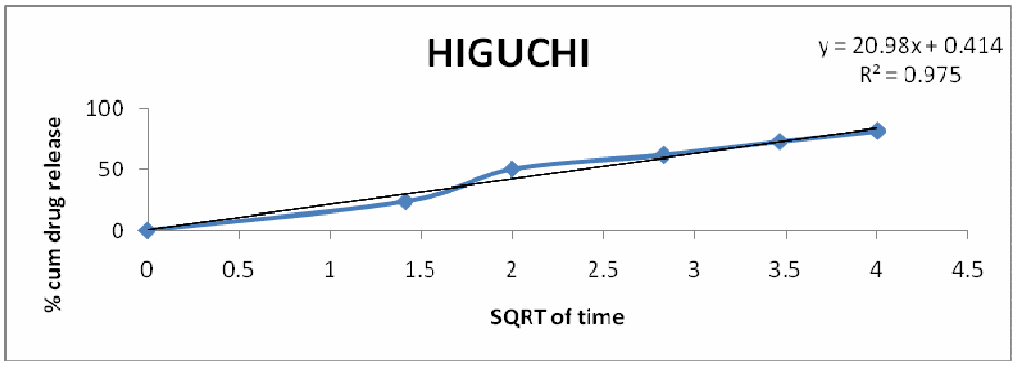


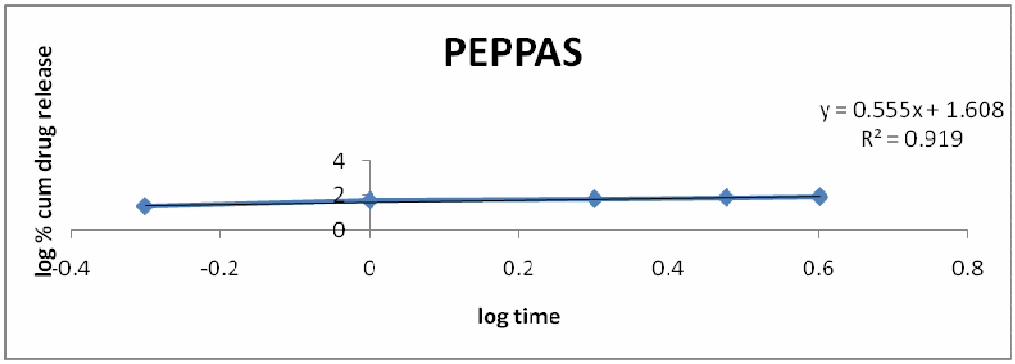


Graph No. 15 : *In-vitro* release kinetic models of **F2**

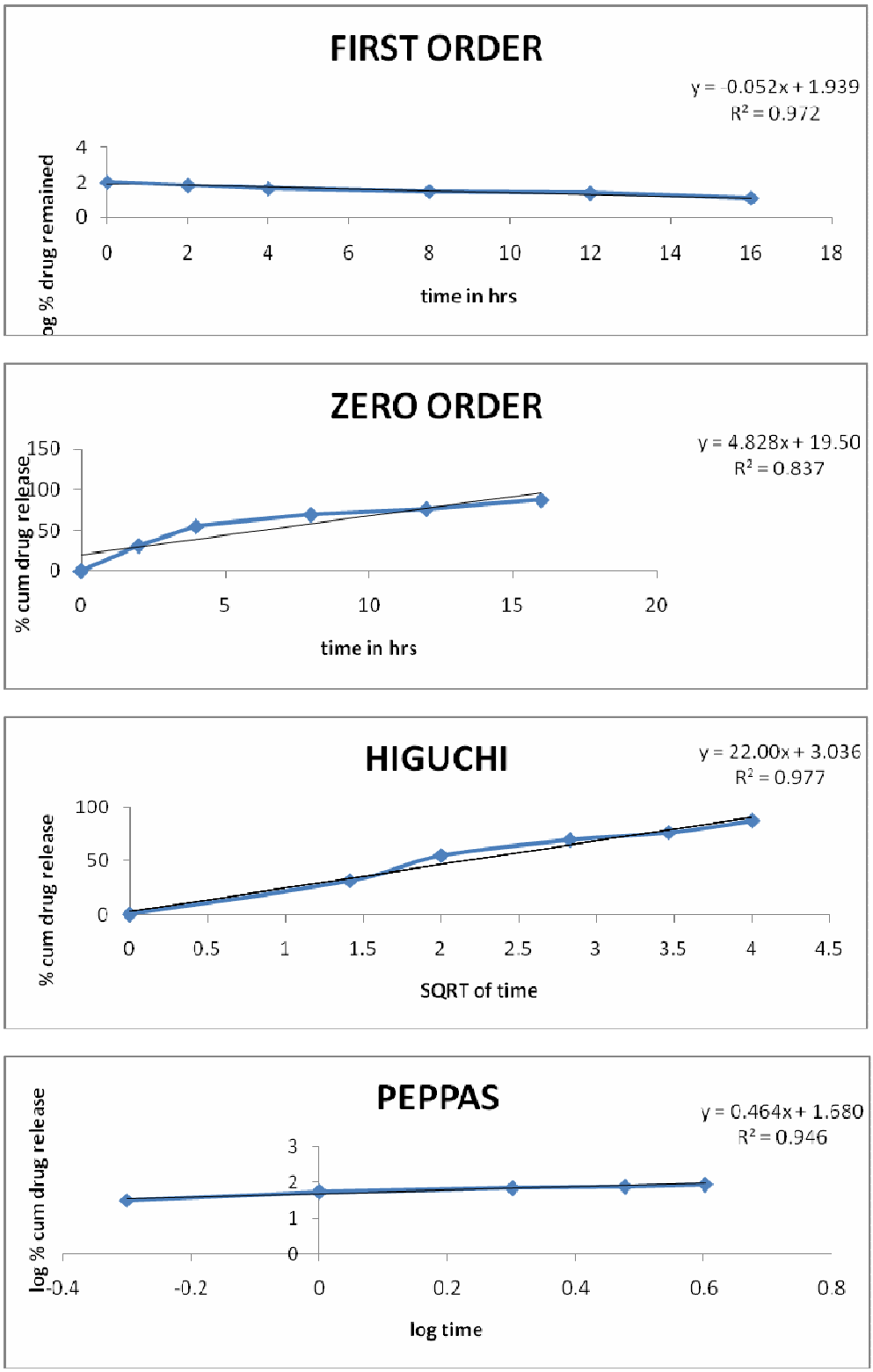




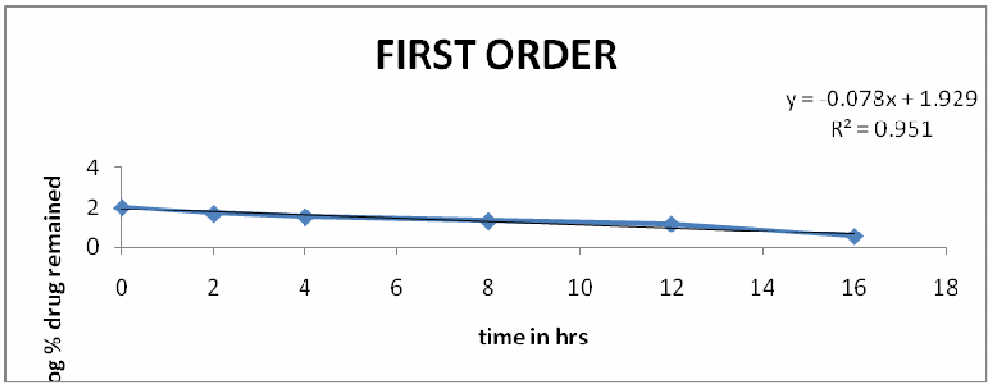


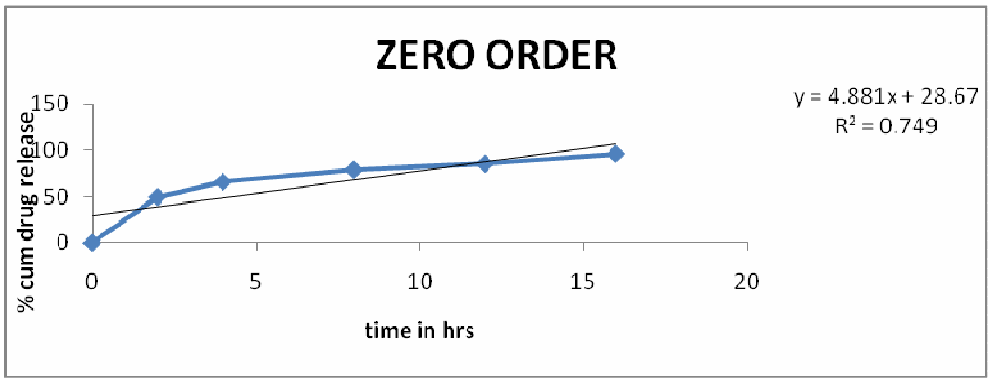


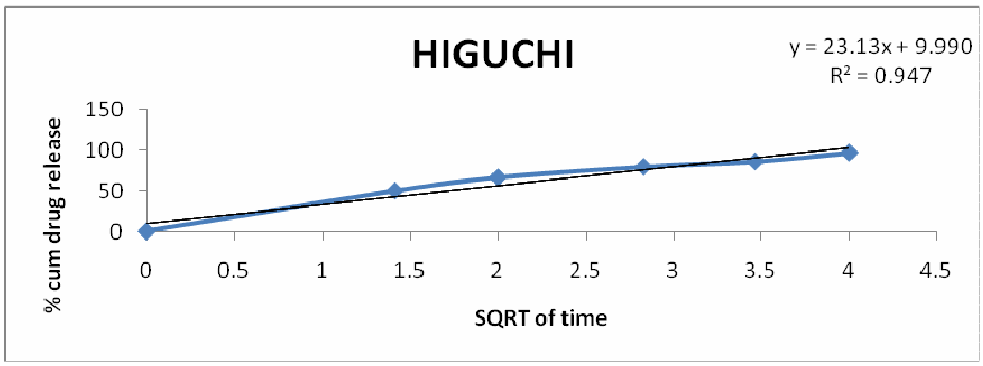
Graph No. 16 : *In-vitro* release kinetic models of **F3**

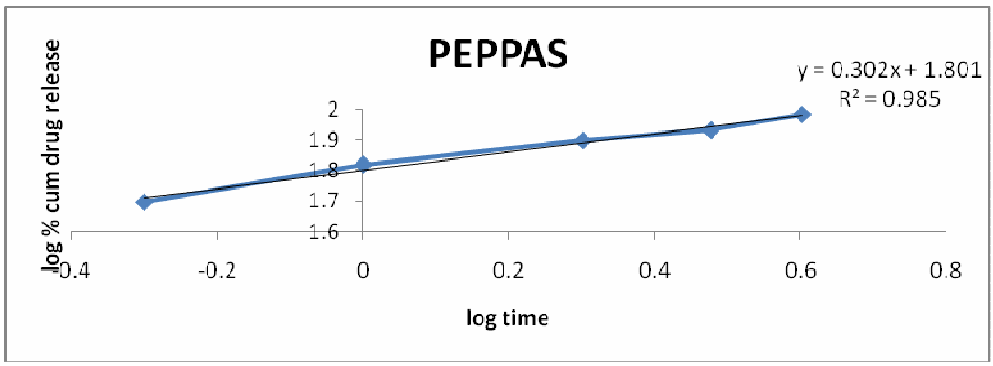


Graph No.17 : *In-vitro* release kinetic models of **F4**

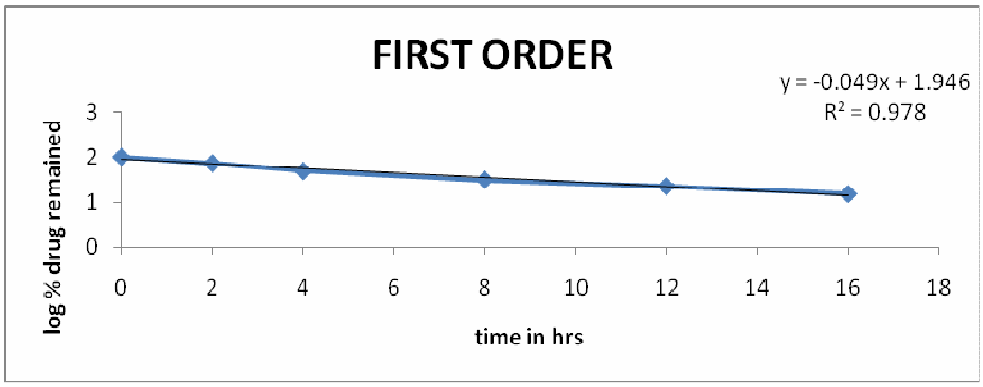


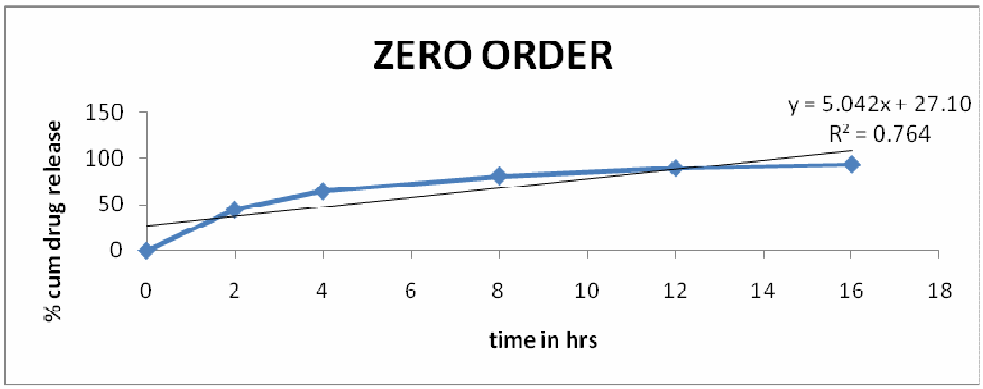


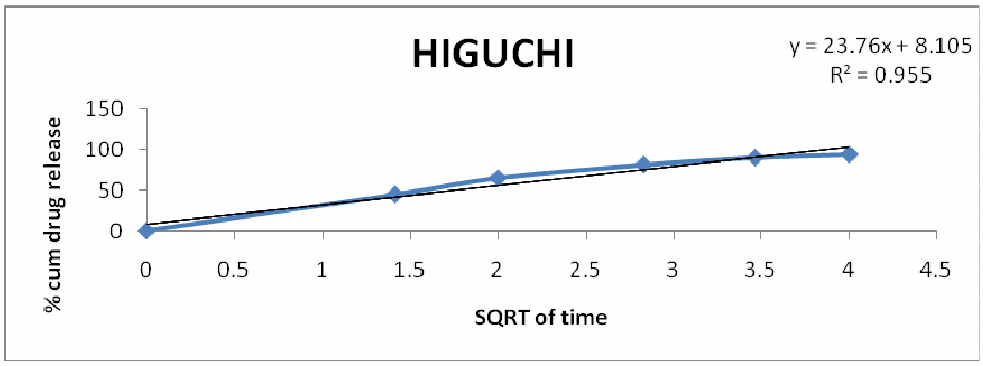


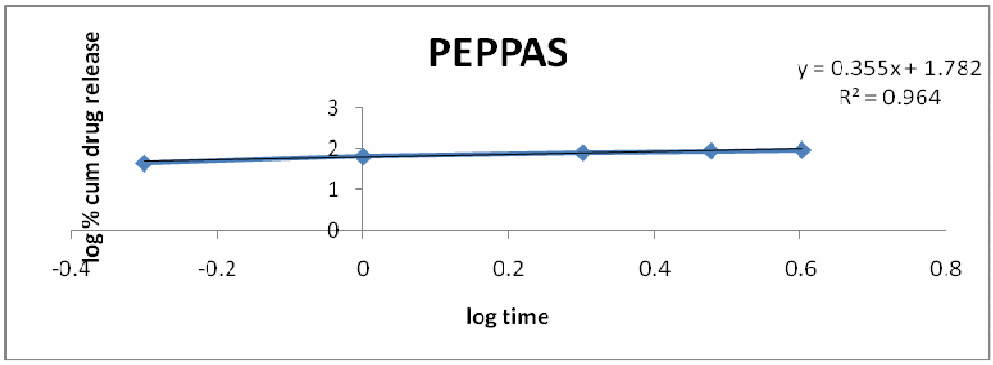


Graph No. 18 : *In-vitro* release kinetic models of **F5:**

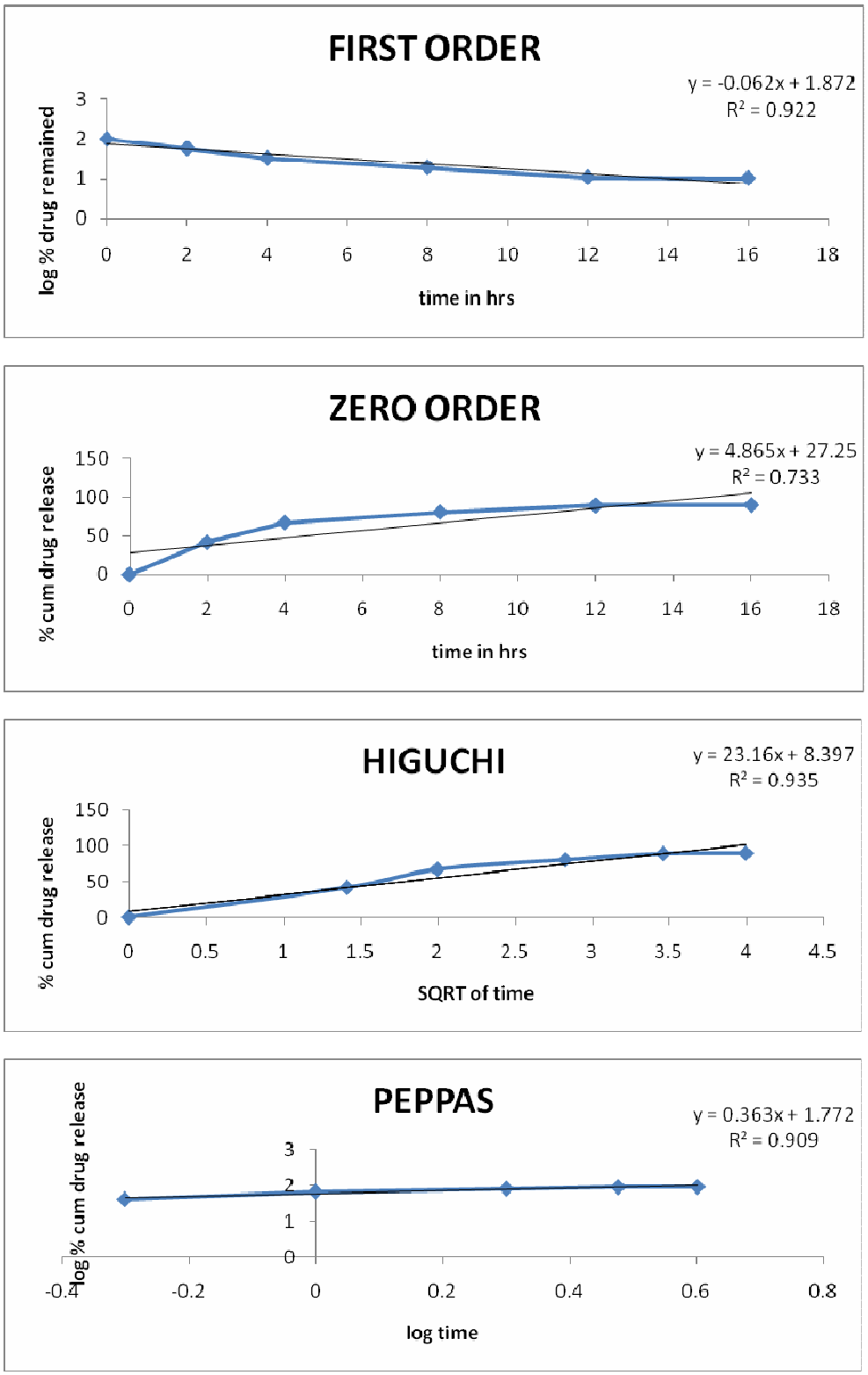




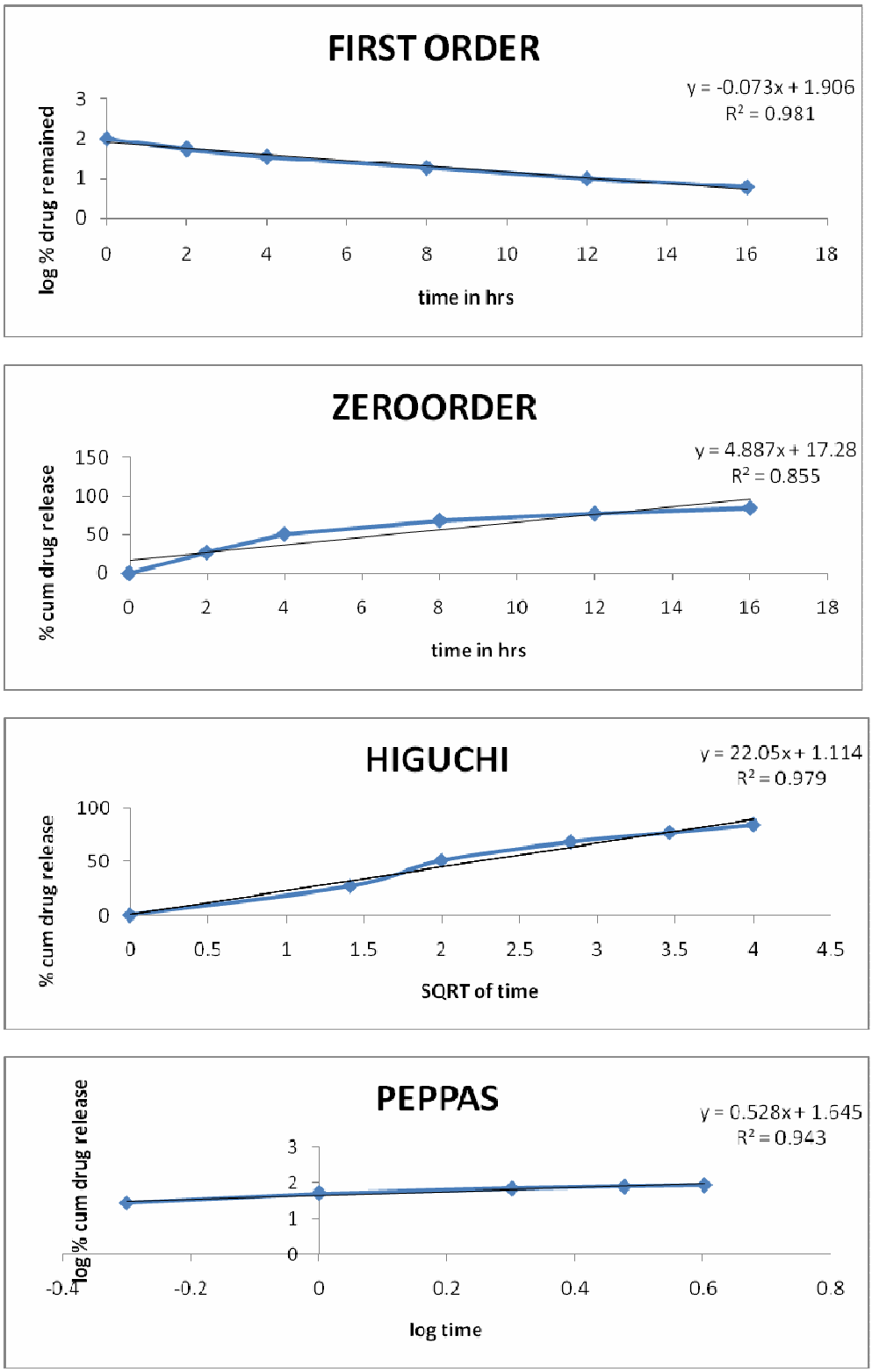




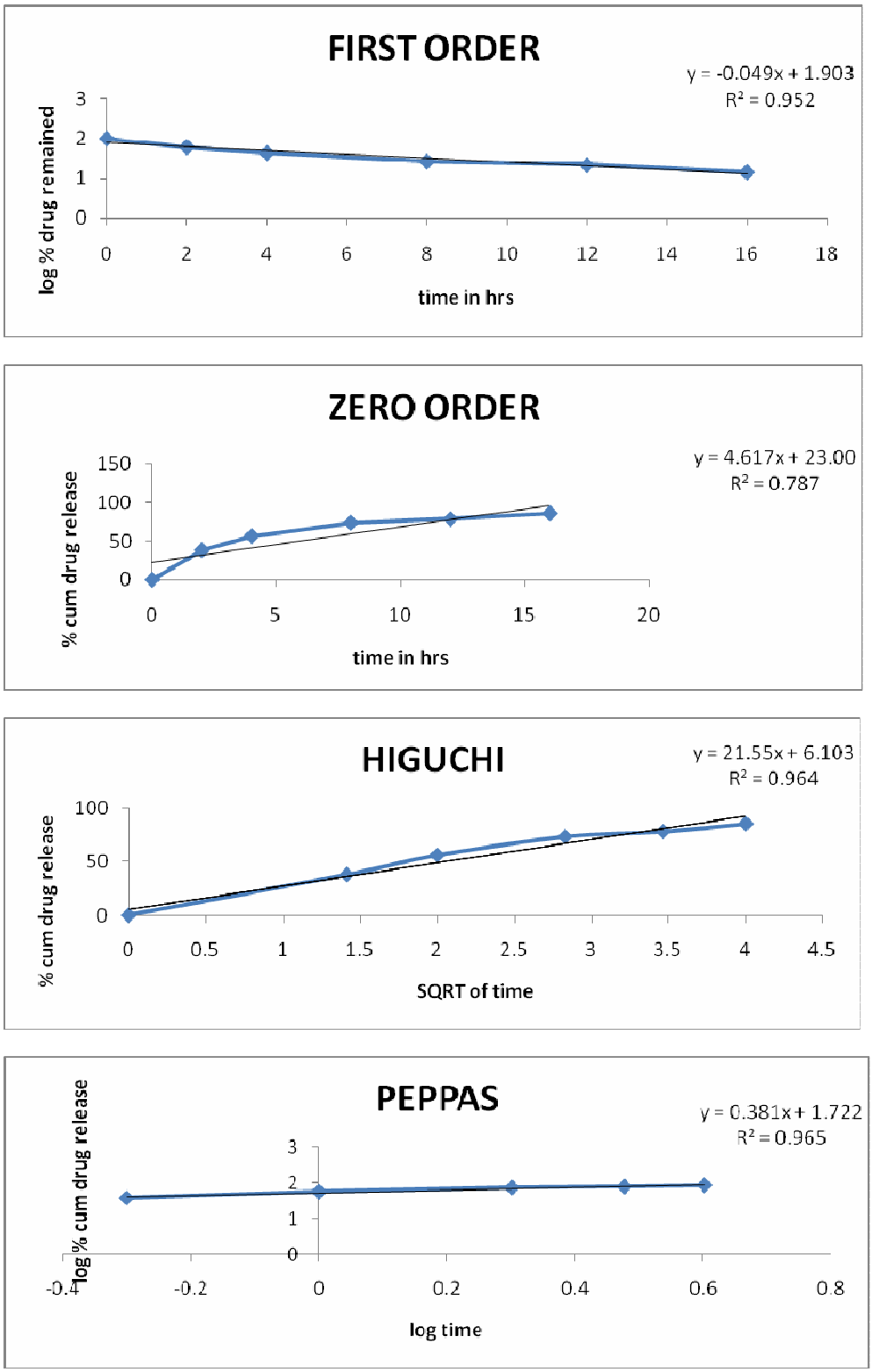
Graph No.19 : *In-vitro* release kinetic models of **F6:**



Graph No. 20 : *In-vitro* release kinetic models of **F7:**



Graph No. 21 : *In-vitro* release kinetic models of **F8**



Graph No. 22 : *In-vitro* release kinetic models of **F9**

Table. No.42: *In-Vitro* Drug Release Kinetic Data

Formulation Code	Mathematical models				
	First Order (R^2)	Zero Order (R^2)	Higuchi Model (R^2)	Peppa's Model (R^2)	'n' value
Innovator	0.923	0.797	0.952	0.814	0.463
F1	0.964	0.871	0.968	0.922	0.648
F2	0.878	0.723	0.928	0.895	0.550
F3	0.973	0.862	0.975	0.919	0.555
F4	0.972	0.837	0.977	0.946	0.464
F5	0.951	0.749	0.947	0.985	0.302
F6	0.978	0.764	0.955	0.964	0.355
F7	0.922	0.733	0.935	0.909	0.363
F8	0.981	0.855	0.979	0.943	0.528
F9	0.952	0.787	0.964	0.965	0.481

The different models, viz. Zero order, first order, higuchi's equation and korsmeyer-peppas equation were used to study the *in-vitro* release of sustained release pellets. The zero order plots of formulations were to be fairly linear as indicated by their high regression values. Therefore, it was ascertained that the drug release from pellets followed either first-order kinetics. The first order curves alone are not sufficient to predict first order since each curve, albeit straight, has a different slope. Hence to confirm the exact mechanism of drug release from the polymer films, the data's were computed and graphed according to Higuchi's equation and korsmeyer-peppas equation.

The release of water-soluble drugs was higher than the drugs with lower solubility and the mechanism of release was changed with the nature and content polymer in the matrix. The type of polymer used imparts a conspicuous on release mechanism.

The amount released in fixed duration was of more importance and were performed with precision and accuracy, the change in amount of polymer was largely dependent on the hydrophilic nature of polymers used in the dissolution study and it suggested many parameters to control for next batches. On increase in the polymer concentration drug release declined.

First order r^2 value for the best batch (F8) was found to be 0.981. Higuchi r^2 Value was found to be 0.979, and peppas r^2 value was found to be 0.943 and 'n' value found to be 0.528 respectively. By the results confirm that order of drug release follows first order and the mechanism of drug release from sustained release pellets was by Non-Fickian diffusion.

Reason for selecting capsules

The Cyclobenzaprine Hydrochloride in tablet form of three times dose per a day the prior art may cause problems in patients with swallowing difficulty for adults and childrens. This drawback is avoided with the use of multi particulate formulations, since they may be dispersed in liquids at the movement of the administration.

It should be kept in mind that pharmaceutical compositions formulated in tablets are subject to variations in their physicochemical properties such as hardness, disintegration time, and dissolution time and also on dissolution rate due to the compression process involved in their production. Such variations are of course undesirable in modified release Cyclobenzaprine Hydrochloride capsules, since the prediction of the dissolution rate is an extremely important factor for the efficiency of the formulation.

Finally sustained release multi particulate formulations of Cyclobenzaprine Hydrochloride of the invention advantageously provide a better drug release at the gastrointestinal tract compared with single tablet formulations and the dosing frequency will be reduced. The sustained release capsules will be used mainly to treat muscle spasm associated with acute, painful musculoskeletal conditions and may improve patient compliance.

7.11. ACCELERATED STABILITY STUDIES

Stability studies are carried out as per ICH guidelines for F8 batch of this product at 40^0C/75%RH for about 3 months in stability chamber.

Stability data for Optimized Formulation F8

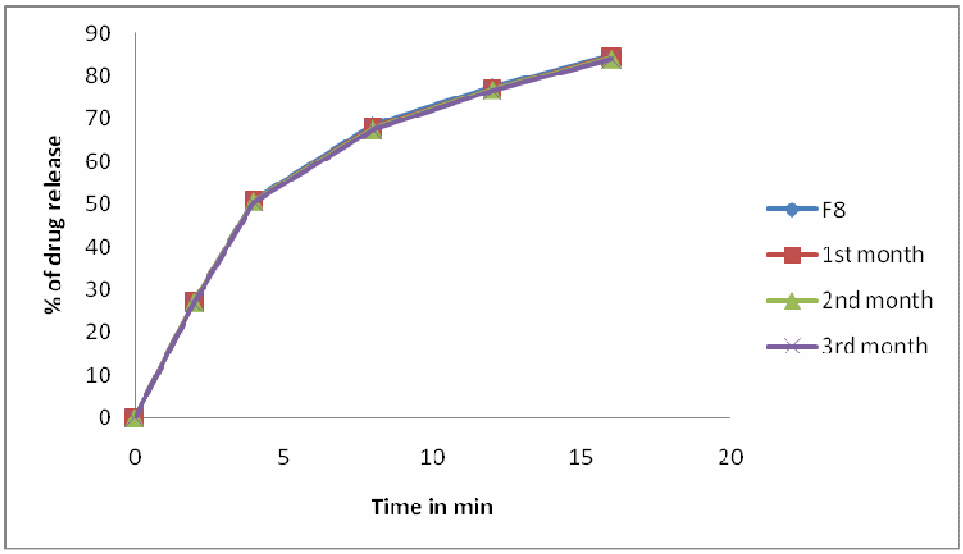
Table No. 44: Evaluation parameter values of stability batch.

Time	Test	Result
End of 1st month	Disintegration time	4.27 min.
	Moisture content	1.76 %
	Assay	99.7%
End of 2ndmonth	Disintegration time	4.28 min.
	Moisture content	1.78 %
	Assay	99.7 %
End of 3rd month	Disintegration time	4.28 min.
	Moisture content	1.78 %
	Assay	99.6 %

No Significant change was observed in the assay and disintegration time and moisture Content values of Cyclobenzaprine hydrochloride capsules, after a storage period of 1st ,2nd, 3rd months at 40^0 C/75 % RH

Table No. 45 Dissolution profile of stability batch at 40°C±2ºC/75% ± 5% RH:

Time (Hrs)	Cumulative Percentage of Drug release at 40°C±2ºC/75% ± 5% RH			
	F8	1st month	2nd month	3rd month
0	0	0	0	0
2	27.2	27.1	27.0	26.8
4	51.1	50.9	50.7	50.6
8	68.6	68.2	67.6	67.5
12	77.4	77.1	76.8	76.5
16	84.7	84.6	84.1	83.9



Graph : 23 Comparision of *In-vitro* release of stability batch with F8

From the above data it was evident that there was no significant change in the physico chemical parameters of Cyclobenzaprine hydrochloride and *in-vitro* release during the stability studies conducted at 40°C & 75%RH for 3 months period when compared with initial samples. So, it has show that formulation F8 was found to be stable one.

8. SUMMARY AND CONCLUSION

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant used in the relief of muscle spasm associated with acute, painful musculoskeletal conditions, and also used as tranquilizing agent, as anti depressant and in the treatment of fibromyalgia.

- *The oral bioavailability of Cyclobenzaprine hydrochloride is 33-55% while its dosing frequency is 3-6 hours. Because of such pharmacokinetic characteristics the conventional dosage forms of the drug suffer the drawbacks of typical immediate release tablets. To overcome these drawbacks, sustained release Pellets can be prepared.*
- *The active pharmaceutical ingredient Cyclobenzaprine Hydrochloride was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with Cyclobenzaprine Hydrochloride drug.*
- Cyclobenzaprine Hydrochloride coated pellets were formulated by using commercially available sugar pellets using the polymers like Ethyl cellulose N-50, HPMC E5, PEG 6000 in different proportions for sustaining release. The optimization procedures aided in the development of formulation of the Cyclobenzaprine Hydrochloride sustained release pellets.

- The method used for the development of pellets was powder layering technique as a simple process. Developed pellets were evaluated for weight variation, percentage friability, assay, moisture content, SEM studies and *in-vitro* drug release as per official procedure and all formulations gave satisfactory results for weight variation, friability and moisture content.

- Among all formulations F8 gave the highest similarity factor (77.5) and better drug release (85.7%) when compare to innovator. F8 was selected as optimized formulation.

- ❖ Drug release profiles were fitted to kinetic modeling like zero order, first order, higuchi and peppas models. It was found that the optimized formulation (F8) was best fitted to first order and followed non-fickian diffusion.

- ❖ SEM studies confirm that the optimized formulation (pellets) have spherical shape and rough surface.

- ❖ The stability of the formulation was determined by "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for moisture content, assay, disintegration and dissolution studies. By the stability studies, the formulated Cyclobenzaprine Hydrochloride sustained release formulation proved to be stable throughout the period of the storage.
- ❖ Sustained release pellets have minimum volume in size, greater surface area and more surface activity. The drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. Because of Small size pellets enter into the systemic circulation in very fast, moreover there was no accumulation of drug in the body.

- ❖ Even though Cyclobenzaprine Hydrochloride tablets and capsules available in market, the formulation of F8 was shows better results when compare to innovator product and the formulation process will be easy, safe and effective.

Thus from the experimental results, it could be finally concluded that the optimized formulated sustained release pellets in capsule of formulation F8 has relevant drug release rate upto 16 hours rather than innovator and it can be used for the relief of muscle spasm associated with acute, painful musculoskeletal conditions.

FUTURE SCOPE:

- *In vivo* evaluation of present study.
- *In vitro – In vivo* correlation studies.
- Development of sustained release dosage form of Cyclobenzaprine Hydrochloride by using other sustained polymers.

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